

PYRIMIDINE DERIVATIVES

5 Technical Field

This invention relates to pyrimidine derivatives or salts thereof which exhibit serotonin receptor subtype 1A ("5-HT_{1A}") agonistic activity and serotonin receptor subtype 3 ("5-HT₃") antagonistic activity concurrently, and which are useful as treating agent of irritable bowel syndrome ("IBS") and the like.

The invention also relates to therapy of IBS and the like, which comprises having the 5-HT_{1A} agonistic activity and 5-HT₃ antagonistic activity synergistically and simultaneously work in vivo.

15 Background Art

IBS is a functional disease of which main symptoms are evacuation abnormalities such as diarrhea or constipation and bellyache, and is not caused by intestinal organic lesion. This disease is developed as the result of mutual association of intestinal motion disorder, viscerosensory anaphylaxis and psychological and social factors.

Because 5-HT₃ in intestine participates in intestinal contraction, secretion of intestinal juice, peristalsis and content transport, diarrheal symptoms can be improved by administration of 5-HT₃ antagonist. In the United States, alosetron which is a 5-HT₃ antagonist has been approved as an IBS treating agent. Also other 5-HT₃ antagonists, for example, ondansetron, alosetron, tropisetron, granisetron and so on are disclosed in WO 99/17755 Pamphlet and US Patent 6,284,770, which publications disclose that 5-HT₃ antagonistic medicines are useful for IBS treating agent.

On the other hand, because psychological and social factors are recognized to be one of the origins of IBS, administration of benzodiazepine antianxiety agent in IBS therapy has been experimented. Recently, novel serotonin agonistic antianxiety agent, for example, non-benzodiazepine compounds showing less adverse

effect are under development and of which application for IBS therapy is expected.

J. Med. Chem., 40, 574-585 (1997) and Eur. J. Med. Chem., 35, 677-689 (2000) disclose pyrimidinone derivatives having selective
5 affinity to 5-HT_{1A}. In these literature references, the derivatives' selectivity for 5-HT_{1A} over α_1 receptor was investigated. Also EP 343,050, WO 01/32659 Pamphlet, JP 2001-97978A and J. Med. Chem., 32, 1147-1156 (1989) disclose piperazinyl isoquinoline derivatives, piperazinyl thienopyridine derivatives and piperazinyl furopyridine
10 derivatives which exhibit affinity to 5-HT_{1A} and the like. While these references describe psychic action based on 5-HT_{1A} agonistic activity, they are silent on 5-HT₃. They contain no disclosure or suggestion on the named derivatives' application to IBS or associated diseases based on their activities on the two receptors.

15 J. Med. Chem., 42, 4362-4379 (1999) discloses piperazinyl-pyrazine derivatives having selective affinity to 5-HT₃, but their action is agonistic.

In Japan, tandospirone which is a 5-HT_{1A} agonist is marketed, of which indication is stress-caused dyspeptic ulcer. This
20 indication is attributable to removal of stress by the antianxiety action of tandospirone, and IBS is not included in its indications.

As above, currently many 5-HT₃ antagonists and 5-HT_{1A} agonists are developed or marketed, but all of these 5-HT₃ antagonists and 5-HT_{1A} agonists have unilateral activities. Because
25 IBS has plural origins, therapeutic effect of these compounds on IBS is insufficient.

Only recently, Bioorg. Med. Chem. Lett., 13, 3177-3180 (2003) disclosed compounds which exhibit affinity to both of the receptors 5-HT₃ and 5-HT_{1A}. These compounds, however, are
30 benzimidazole-arypiperazine derivatives, and the literature refers only to the compounds' action on nervous system, containing no disclosure or suggestion on combination of 5-HT₃ antagonistic activity and 5-HT_{1A} agonistic activity on IBS or the effect based on the combination.

35 We have engaged in concentrative studies to discover

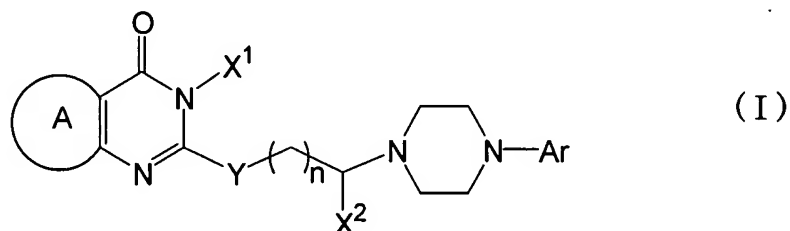
simultaneous expression in vivo of 5-HT₃ antagonistic activity and 5-HT_{1A} agonistic activity is very effective for treating the diseases associated with both hyperactivity or expression enhancement of 5-HT₃ and hypoactivity of 5-HT_{1A}, in particular, treating IBS.

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Disclosure of the Invention

Thus, the present invention provides novel pyrimidine derivatives represented by the following formula (I)

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in which

ring A stands for a carbocyclic group or heterocyclic group,

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X¹ stands for hydrogen, amino, lower alkylamino, di-lower alkylamino, lower alkylideneamino, lower alkyl, phenyl lower alkyl or substituted or unsubstituted phenyl,

X² stands for hydrogen or lower alkyl,

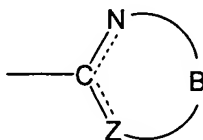
Y stands for a direct bond, sulfur or nitrogen,

n is 0 or an integer of 1 – 4,

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Ar stands for a group represented by the following formula,

30



which is either unsubstituted or substituted with substituent(s) selected from halogen, lower alkyl, hydroxyl, lower alkoxy and phenyl, and in which

Z stands for carbon, oxygen or sulfur,

35

B stands for the residual member(s) necessary for

completing a monocyclic or polycyclic, nitrogen-containing heterocyclic ring group, which may form a condensed ring together with the remainder of the group of the above formula, and the dotted lines indicate optionally existing bonds,

5 or their pharmaceutically acceptable salts, which concurrently possess 5-HT_{1A} agonistic activity and 5-HT₃ antagonistic activity.

The invention also provides a therapeutic method of IBS characterized by exerting 5-HT_{1A} agonistic activity and 5-HT₃ antagonistic activity in vivo simultaneously and cooperatively, which
 10 comprises administering to human being or other mammals who require IBS treatment, 5-HT₃ antagonistic agent concurrently exhibiting 5-HT_{1A} agonistic activity, or administering 5-HT_{1A} agonistic agent and 5-HT₃ antagonistic agent simultaneously, or in sequence, or at an interval.

15 Hereinafter the invention is explained in further details.

In the present specification, the term "lower" means that the groups referred to by this term have not more than six carbons, preferably not more than 4 carbons.

20 "Lower alkyl" has either straight chain or branched chain structure, examples of which including methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl and n-hexyl. Of those, C₁ – C₄ alkyl such as methyl, ethyl, n-propyl, isopropyl and n-butyl are preferred. As "lower alkoxy", for example, methoxy,
 25 ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutyloxy, sec-butyloxy, n-pentyloxy and n-hexyloxy can be named, among which C₁ – C₄ alkoxy such as methoxy, ethoxy, n-propoxy, isopropoxy and n-butoxy are preferred.

"Phenyl lower alkyl" in the definition of X¹ signifies lower
 30 alkyl as exemplified in the above, which are substituted with phenyl, examples of which including benzyl, phenylethyl, phenylpropyl and phenylbutyl. Of these, benzyl is particularly preferred. Also as the substituent on phenyl of "substituted or unsubstituted phenyl" in the definition of X¹, for example, halogen, lower alkyl and lower alkoxy
 35 can be named, among which lower alkoxy is preferred.

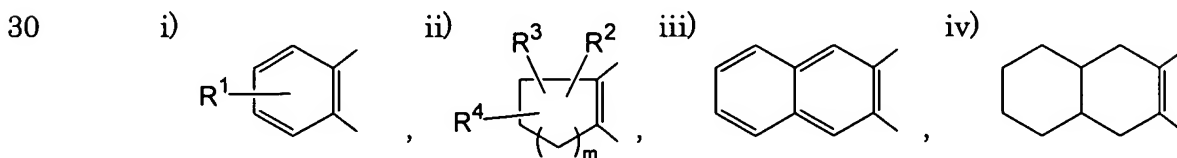
“Lower alkylamino” in the definition of X^1 signifies amino which is mono-substituted with lower alkyl as above exemplified, specific examples including N-methylamino, N-ethylamino, N-n-propylamino, N-isopropylamino, N-n-butylamino, N-isobutylamino, N-sec-butylamino, N-tert-butylamino, N-n-pentylamino and N-n-hexylamino. Of these, $C_1 - C_4$ alkylamino such as N-methylamino, N-ethylamino, N-n-propylamino, N-isopropylamino and N-n-butylamino are particularly preferred.

“Di-lower alkylamino” in the definition of X^1 signifies amino which is di-substituted with same or different lower alkyl as above exemplified, specific examples including N,N-dimethylamino, N,N-diethylamino, N,N-di-n-propylamino, N,N-diisopropylamino, N-methyl-N-ethylamino, N-methyl-N-n-propylamino, N-ethyl-N-isopropylamino, N-methyl-N-n-butylamino, N-ethyl-N-isobutylamino, N-isopropyl-N-sec-butylamino, N-n-propyl-N-n-pentylamino and N-methyl-N-n-hexylamino. Of these, di- $C_1 - C_4$ alkylamino such as N,N-dimethylamino, N-methyl-N-ethylamino, N-ethyl-N-isopropylamino and N-methyl-N-n-butylamino are particularly preferred.

“Lower alkylideneamino” in the definition of X^1 signifies amino which is substituted with lower alkylidene, specific examples including N-isopropylideneamino.

“Halogen” includes fluorine, chlorine, bromine and iodine, among which fluorine, chlorine and bromine are particularly preferred.

Where the ring A in the formula (I) stands for carbocyclic group, preferred examples of the carbocyclic group include those represented by the following formulae i) – iv),



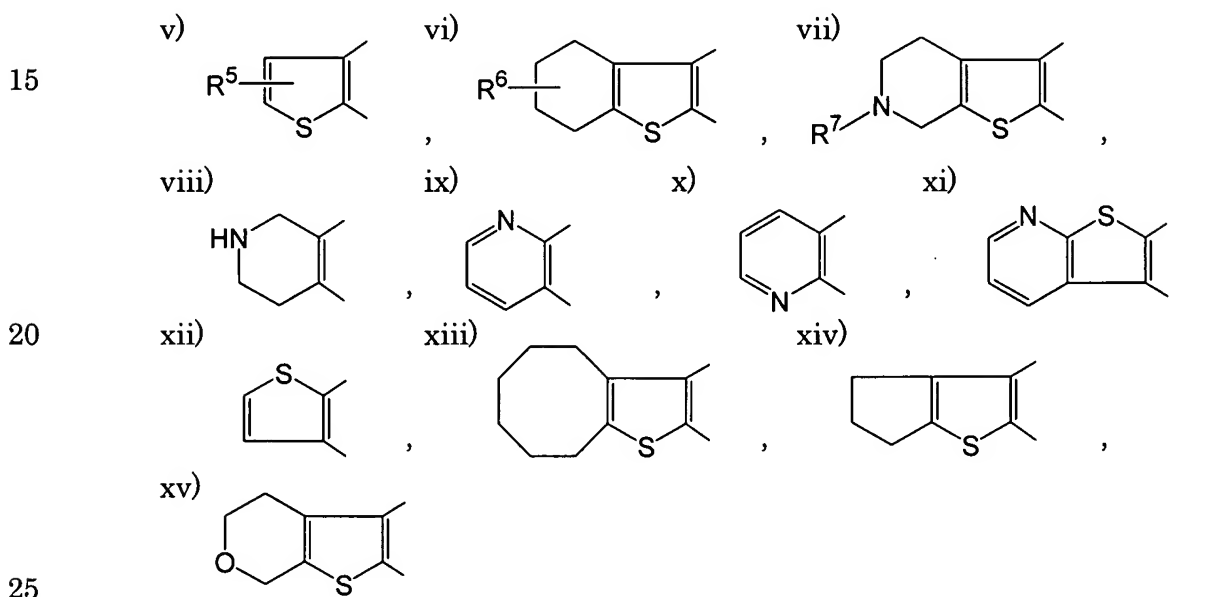
35 in which

R^1 stands for hydrogen, halogen, lower alkyl, halogenated lower alkyl, lower alkoxy, carboxyl, lower alkoxycarbonyl, phenyl, amino, hydrazino or nitro,

R^2 , R^3 and R^4 either stand for, independently from each other, hydrogen, halogen, lower alkyl, lower alkoxy, phenyl or hydroxyl; or two out of R^2 , R^3 and R^4 together stand for oxo or lower alkylenedioxy, and

m is an integer of 1 – 3.

Where the ring A in the formula (I) stands for heterocyclic group, the heterocyclic group may be a monocycle or may form a condensed ring with another ring, preferred examples of which include those of the following formulae v) – xv),



in which

R^5 stands for hydrogen, lower alkyl, carboxyl or lower alkoxycarbonyl,

R^6 stands for hydrogen or lower alkyl, and

R^7 stands for hydrogen, lower alkyl, lower alkanoyl, lower alkoxycarbonyl or phenyl lower alkoxycarbonyl.

As the ring A, groups of the formula i) or ii) are preferred, those of the formula ii) being particularly preferred.

In the above definition of ring A, "halogenated lower alkyl" signifies lower alkyl whose at least one hydrogen is substituted with halogen, examples of which including chloromethyl, 2-bromoethyl, 3-fluoropropyl, 4-iodoisopentyl, dichloromethyl, 1,2-dibromoethyl, 5 trifluoromethyl and 2,2,2-trichloroethyl. Of these, chloromethyl and trifluoromethyl are particularly preferred.

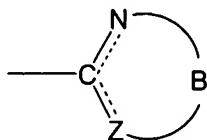
"Lower alkoxy-carbonyl" in the definition of ring A signifies lower alkoxy-CO-group, for example, methoxycarbonyl, ethoxy-carbonyl, isopropoxycarbonyl and tert-butoxycarbonyl. Of these, 10 methoxycarbonyl and ethoxycarbonyl are particularly preferred.

As examples of "lower alkylenedioxy" in the definition of ring A, methylenedioxy, ethylenedioxy and trimethylenedioxy can be named, ethylenedioxy being particularly preferred.

"Lower alkanoyl" in the definition of ring A signifies lower 15 alkyl-CO-group, for example, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl or pivaloyl. Of these, acetyl and propionyl are particularly preferred.

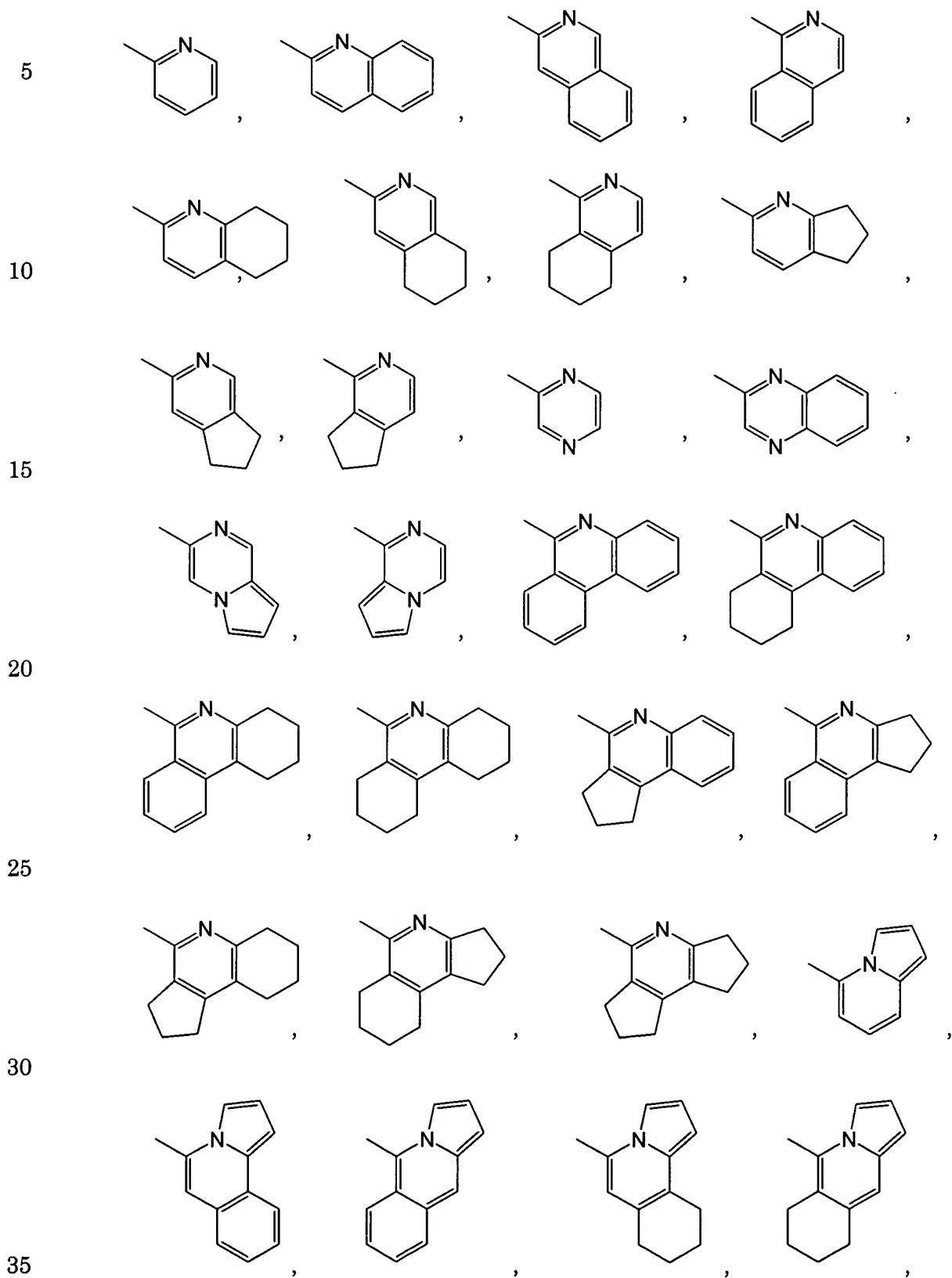
"Phenyl lower alkoxy-carbonyl" in the definition of ring A signifies lower alkoxy-carbonyl as explained in the above, which is 20 substituted with phenyl, for example, benzyloxycarbonyl, 1-phenylethoxycarbonyl, 2-phenylethoxycarbonyl, 3-phenylpropoxy-carbonyl, 1-benzylethoxycarbonyl or 1-benzyl-1-methylethoxy-carbonyl. Of these, benzyloxycarbonyl, 2-phenylethoxycarbonyl and 3-phenylpropoxycarbonyl are preferred.

25 The group represented by the formula,

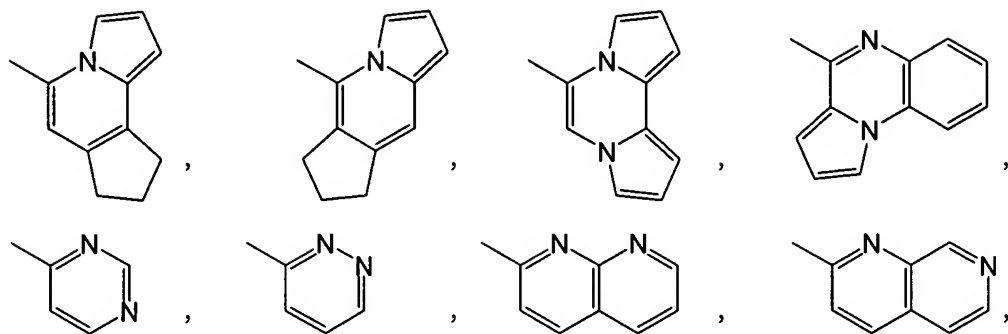


30 in which Z and B have the previously given significations, in the definition of Ar in the formula(I) includes, for example, monocyclic or polycyclic, nitrogen-containing heterocyclic groups which are either unsubstituted or substituted with a substituent 35 selected from halogen, lower alkyl, hydroxyl, lower alkoxy and phenyl.

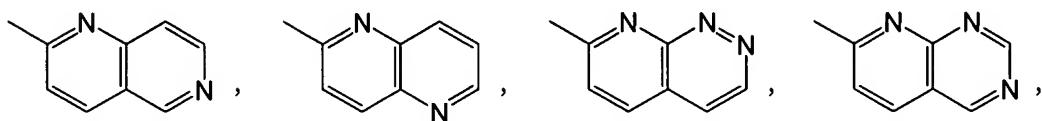
As the skeletal structure of the nitrogen-containing heterocyclic group, those of the following formulae,



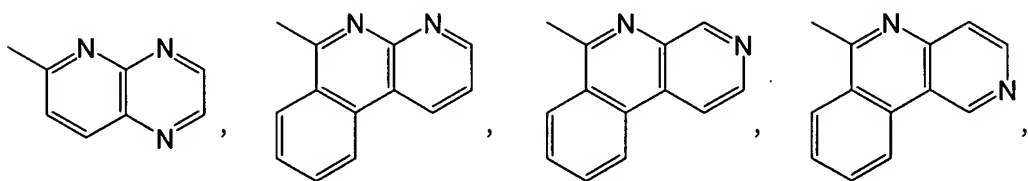
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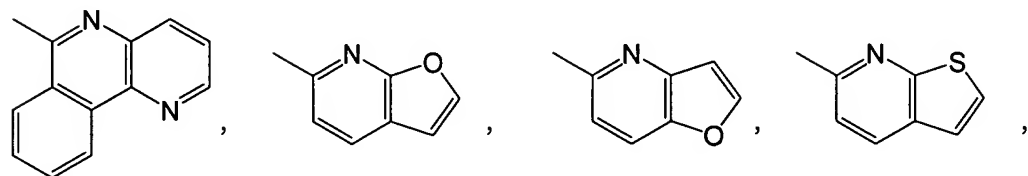
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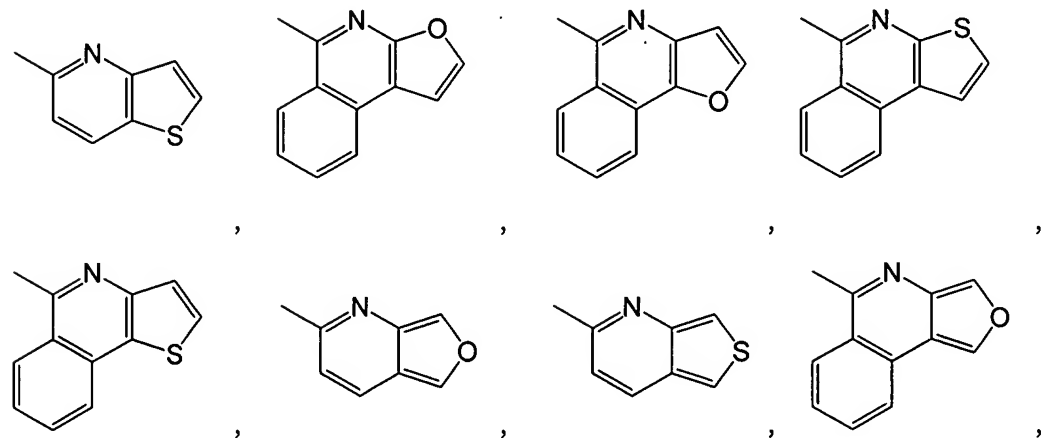
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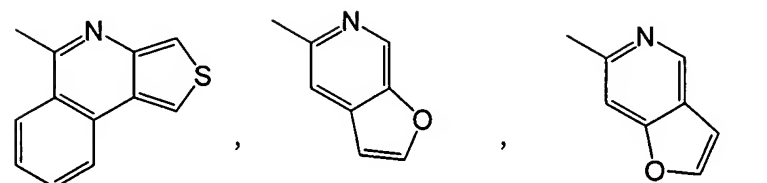
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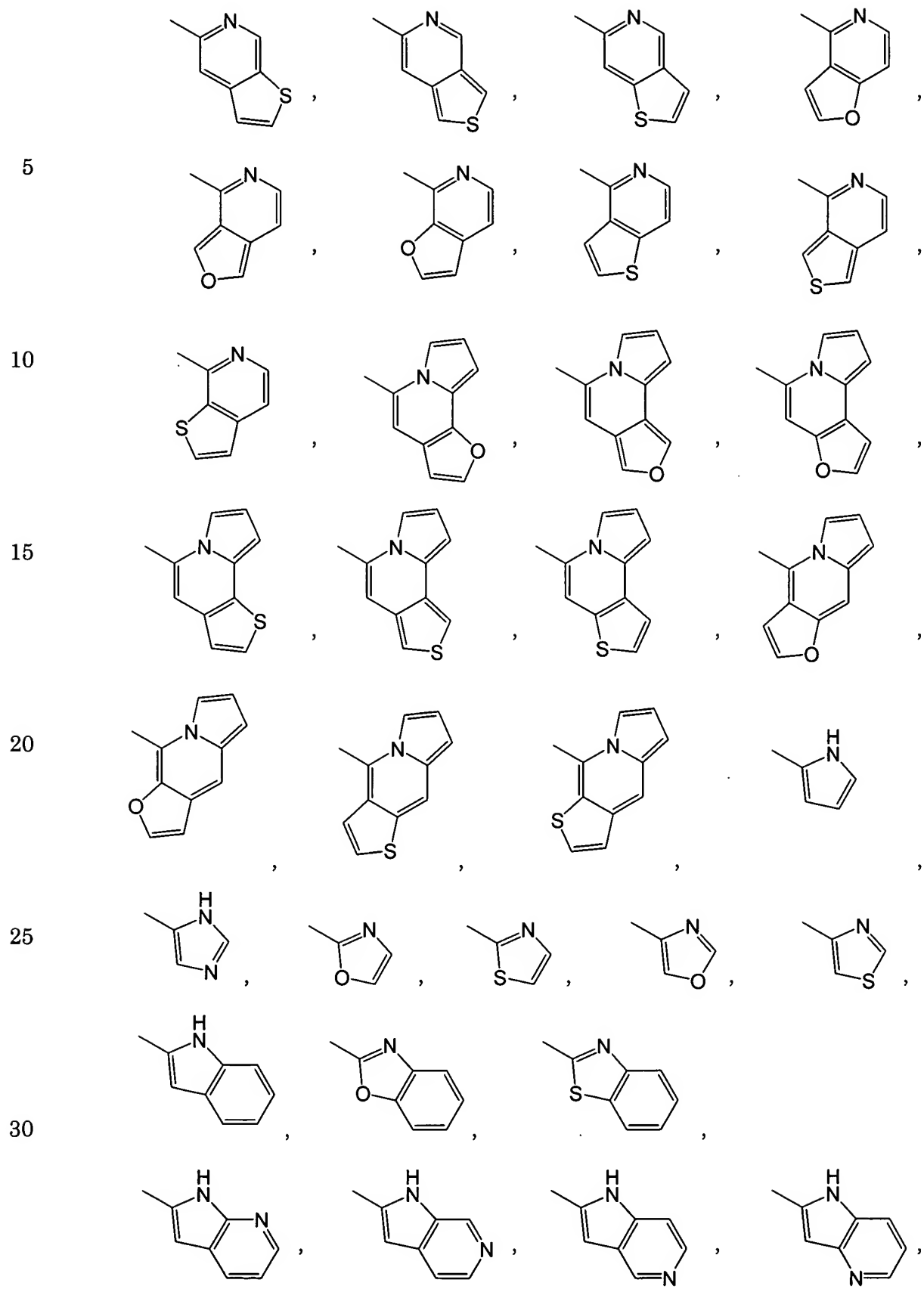
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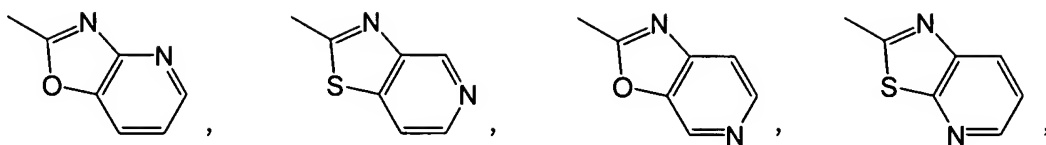


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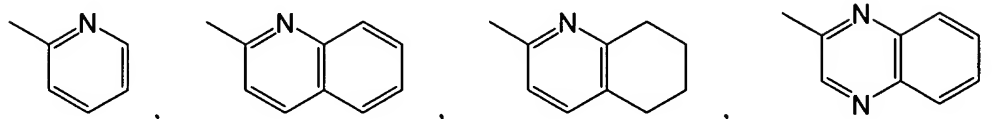
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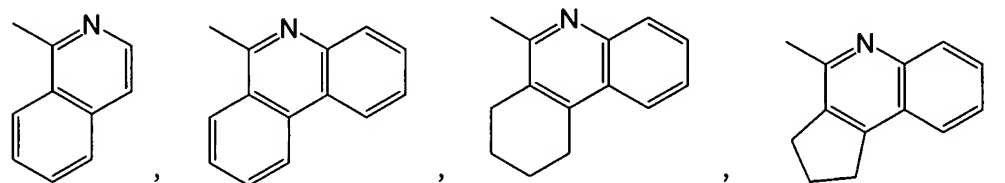


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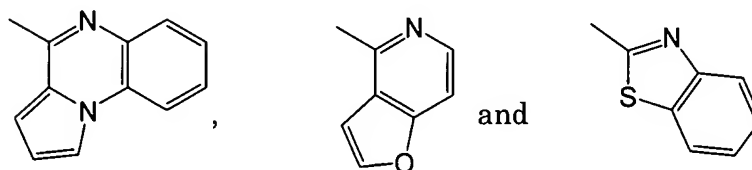
can be named. Of these, those of the following formulae,



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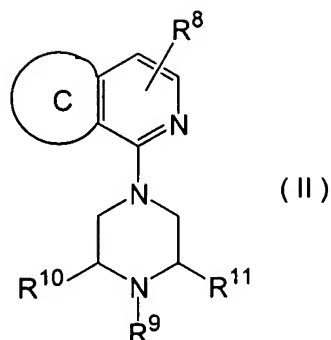
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are particularly preferred.

“5-HT₃ antagonistic agent concurrently exhibiting 5-HT_{1A} agonistic activity” in the present specification may have still other pharmacological activity(ies) in addition to 5-HT_{1A} agonistic activity and 5-HT₃ antagonistic activity. More specifically, as examples of such antagonistic agent, pyrimidine derivatives represented by the given formula (I) and pharmaceutically acceptable salts thereof, and piperazinyipyridine derivatives represented by the following formula (II),



in which

ring C stands for unsubstituted benzene ring or an unsubstituted heterocyclic group selected from pyridine, furan and thiophene; benzene ring substituted with substituent(s) selected from halogen, lower alkyl, phenyl, hydroxyl, lower alkoxy, phenyl lower alkoxy (the phenyl moiety being either unsubstituted or halogen-substituted), amino, lower alkylamino, di-lower alkylamino, lower alkylthio, lower alkylsulfinyl and aminosulfonyloxy; or heterocyclic group selected from halogen- or lower alkyl-substituted pyridine, furan and thiophene,

R^8 stands for hydrogen, halogen or lower alkyl,

R^9 stands for hydrogen, lower alkyl, phenyl lower alkyl (the phenyl moiety being unsubstituted or substituted with substituent(s) selected from halogen, lower alkyl and lower alkoxy), amino lower alkyl (the amino moiety being either unsubstituted or mono- or di-substituted with lower alkyl, or optionally forming a cyclic imido group) or phenyl cycloalkyl (the phenyl moiety being either unsubstituted or substituted with substituent(s) selected from halogen, lower alkyl and lower alkoxy),

R^{10} stands for hydrogen or lower alkyl, or

R^9 and R^{10} may together form the residual members of pyrrolidine ring or piperidine ring (which may be unsubstituted or substituted with substituent(s) selected from hydroxyl, lower alkoxy and phenyl lower alkoxy), and

R^{11} stands for hydrogen or lower alkyl,

or their pharmaceutically acceptable salts can be named.

“Phenyl lower alkoxy (the phenyl moiety being either unsubstituted or halogen-substituted)” in the definition of ring C in the formula (II) signifies lower alkoxy which is substituted with unsubstituted or halogen-substituted phenyl, examples of which including benzyloxy, phenylethoxy, phenylpropyloxy, phenylbutoxy, 2-chlorobenzyloxy, 2-bromobenzyloxy, 2-fluorobenzyloxy, 3-bromobenzyloxy, 4-fluorobenzyloxy, 2,4-dichlorobenzyloxy and 1-(4-fluorophenylmethyl)ethoxy. Of these, unsubstituted benzyloxy and benzyloxy substituted with one halogen atom are particularly preferred.

“Lower alkylamino” in the definition of ring C in the formula (II) signifies amino which is mono-substituted with lower alkyl, examples of which including N-methylamino, N-ethylamino, N-n-propylamino and N-sec-butylamino. Of these, N-methylamino and N-ethylamino are particularly preferred. Also “di-lower alkylamino” in the definition of ring C signifies amino which is di-substituted with same or different lower alkyl groups, examples of which including N,N-dimethylamino, N,N-diethylamino, N,N-diisopropylamino, N-methyl-N-ethylamino and N-methyl-N-tert-butylamino. Of these, N,N-dimethylamino and N,N-diethylamino are particularly preferred.

“Lower alkylthio” in the definition of ring C in the formula (II) signifies lower alkyl-S-group, examples of which including methylthio, ethylthio and isobutylthio. Of these, methylthio is particularly preferred. “Lower alkylsulfinyl” in the definition of ring C signifies lower alkyl-SO- group, examples of which including methylsulfinyl, ethylsulfinyl and isopropylsulfinyl. Of these, methylsulfinyl is particularly preferred.

Furthermore, where the ring C in the formula (II) stands for “unsubstituted heterocyclic group selected from pyridine, furan and thiophene” or “heterocyclic group selected from pyridine, furan and thiophene”, as the heterocyclic ring formed by condensation of such ring C with the pyridine ring in the formula (II), for example, 1,6-naphthyridine, 2,6-naphthyridine, 2,7-naphthyridine, 1,7-naphthyridine, furo[3,2-c]pyridine, furo[3,4-c]pyridine,

furo[2,3-c]pyridine, thieno[3,2-c]pyridine, thieno[3,4-c]pyridine and thieno[2,3-c]pyridine can be named. Of these, 1,6-naphthyridine, 2,6-naphthyridine, 2,7-naphthyridine, 1,7-naphthyridine, furo[3,2-c]pyridine, furo[2,3-c]pyridine, thieno[3,2-c]pyridine and thieno[2,3-c]pyridine are preferred, in particular, 1,6-naphthyridine, 1,7-naphthyridine, furo[2,3-c]pyridine and thieno[2,3-c]pyridine are preferred.

“Phenyl lower alkyl (the phenyl moiety being unsubstituted or substituted with a substituent selected from halogen, lower alkyl and lower alkoxy)” in the definition of R⁹ in the formula (II) signifies lower alkyl which is substituted with substituted or unsubstituted phenyl. As the substituent on the phenyl, for example, 2-fluoro, 3-fluoro, 4-fluoro, 2-chloro, 4-chloro, 3-bromo, 4-bromo, 4-iodo, 2-methyl, 3-methyl, 4-methyl, 2-ethyl, 3-ethyl, 3-n-propyl, 4-isopropyl, 2-methoxy, 3-methoxy, 4-methoxy, 3-ethoxy and 4-isopropoxy can be named. Of these, 4-fluoro, 4-chloro, 4-bromo, 3-methyl, 3-ethyl, 3-methoxy and 3-ethoxy are preferred. Also as the lower alkyl in the above definition, for example, methyl, ethyl, n-propyl and n-butyl are preferred. Thus, as preferred specific examples of “phenyl lower alkyl (the phenyl moiety being either unsubstituted or substituted with a substituent selected from halogen, lower alkyl and lower alkoxy)”, benzyl, 4-fluorobenzyl, 2-(4-chlorophenyl)ethyl, 3-(4-bromophenyl)-n-propyl, 3-methylbenzyl, 3-(3-ethylphenyl)butyl, 3-methoxybenzyl and 4-(3-methoxyphenyl)butyl can be named.

“Amino lower alkyl (the amino moiety being either unsubstituted or mono- or di-substituted with lower alkyl, or may form cyclic imido)” in the definition of R⁹ in the formula (II) signifies lower alkyl substituted with amino, wherein the “amino” includes not only unsubstituted amino but also amino which is substituted with one or two lower alkyl groups and amino which formed cyclic imido. As preferred lower alkyl substituent on the amino, methyl, ethyl, n-propyl and n-butyl can be named. Thus, as preferred specific examples of “amino lower alkyl (the amino moiety being either unsubstituted or mono- or di-substituted with lower alkyl, or may form cyclic imido)”, aminomethyl, 2-aminoethyl, 3-aminopropyl,

4-aminobutyl, 2-(N-methylamino)ethyl, 3-(N,N-dimethylamino)propyl and 3-phthaliminopropyl can be named.

Again, "phenyl cycloalkyl (the phenyl moiety being either unsubstituted or substituted with a substituent selected from
 5 halogen, lower alkyl and lower alkoxy)" in the definition of R⁹ of the formula (II) signifies cycloalkyl which is substituted with unsubstituted phenyl or substituted phenyl with a substituent selected from halogen, lower alkyl and lower alkoxy, wherein the substituent on the phenyl can be any of those named as examples of
 10 substituents on the phenyl group in "phenyl lower alkyl" in the definition of R⁹. As the cycloalkyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like can be named, among which cyclohexyl is preferred. As the substitution site of the phenyl in the "phenyl cycloalkyl", 3-position is preferred for cyclopentyl, 4-position
 15 is preferred for cyclohexyl and cycloheptyl, and 5-position is preferred for cyclooctyl. Thus, as preferred specific examples of "phenyl cycloalkyl (the phenyl moiety being either unsubstituted or substituted with a substituent selected from halogen, lower alkyl and lower alkoxy)", 4-(4-fluorophenyl)cyclohexyl,
 20 4-(4-chlorophenyl)cyclohexyl, 4-(4-bromophenyl)cyclohexyl, 4-(3-methylphenyl)cyclohexyl, 4-(3-ethylphenyl)cyclohexyl, 4-(3-methoxyphenyl)cyclohexyl and 4-(3-ethoxyphenyl)cyclohexyl can be named.

As the substituent on the benzene ring in the isoquinoline
 25 ring which is formed when ring C in the formula (II) stands for benzene ring, for example, 5-chloro, 6-chloro, 7-chloro, 8-chloro, 5-fluoro, 7-fluoro, 5-bromo, 7-bromo, 5-iodo, 5-methyl, 6-methyl, 7-methyl, 8-methyl, 5-ethyl, 5-n-propyl, 5-sec-butyl, 5-phenyl, 6-phenyl, 7-phenyl, 8-phenyl, 5-hydroxy, 6-hydroxy, 7-hydroxy,
 30 8-hydroxy, 5-methoxy, 6-methoxy, 7-methoxy, 8-methoxy, 5-ethoxy, 7-ethoxy, 5-isopropoxy, 5-tert-butyloxy, 5-benzyloxy, 7-benzyloxy, 5-(2-phenyl)ethoxy, 5-(4-fluorophenyl)methoxy, 7-(4-fluorophenyl)-methoxy, 5-(2-chlorophenyl)methoxy, 5-(3-bromophenyl)methoxy, 5-(2-fluoro-4-chlorophenyl)methoxy, 6-(2,4-dichlorophenyl)ethoxy,
 35 5-amino, 6-amino, 7-amino, 8-amino, 5-(N-methylamino),

7-(N-methylalmino), 5-(N-ethylamino), 5-(N-isobutylamino),
 6-(N-tert-butylamino), 5-(N,N-dimethylamino), 7-(N,N-dimethyl-
 amino), 5-(N,N-diisopropylamino), 6-(N-methyl-N-n-butylamino),
 5-methylthio, 6-methylthio, 7-methylthio, 8-methylthio, 5-ethylthio,
 5 5-n-propylthio, 5-isobutylthio, 6-isopropylthio, 5-methylsulfinyl,
 6-methylsulfinyl, 7-methylsulfinyl, 8-methylsulfinyl, 5-ethylsulfinyl,
 6-isopropylsulfinyl, 7-tert-butylsulfinyl, 8-n-pentylsulfinyl,
 5-aminosulfonyloxy, 6-aminosulfonyloxy, 7-aminosulfonyloxy and
 8-aminosulfonyloxy can be named. Of these, 5-chloro, 6-chloro,
 10 7-chloro, 7-fluoro, 7-bromo, 7-methyl, 7-phenyl, 7-hydroxy, 5-methoxy,
 6-methoxy, 7-methoxy, 7-ethoxy, 7-benzyloxy, 7-(4-fluorophenyl)-
 methoxy, 7-(N-methylamino), 7-(N,N-dimethylamino), 7-methylthio,
 7-methylsulfinyl and 7-aminosulfonyloxy are preferred. In
 particular, 6-chloro, 7-chloro, 7-fluoro, 7-bromo, 7-methyl, 7-hydroxy,
 15 7-methoxy, 7-ethoxy, 7-benzyloxy, 7-(4-fluorophenyl)methoxy,
 7-(N,N-dimethylamino) and 7-methylthio are preferred.

Also as the substituent on the pyridine ring in the
 isoquinoline ring which is formed when the ring C in the formula (II)
 stands for benzene ring, i.e., as the group R⁸ in the formula (II), for
 20 example, 3-fluoro, 4-fluoro, 3-chloro, 4-chloro, 3-bromo, 4-bromo,
 3-iodo, 4-iodo, 3-methyl, 4-methyl, 3-ethyl, 4-ethyl, 3-n-propyl,
 4-isopropyl, 3-tert-butyl, 4-n-butyl, 3-isopentyl and 4-(1,2-dimethyl-
 butyl) can be named. Of these, 3-chloro, 4-chloro, 3-methyl and
 4-methyl are preferred. Thus, as the preferred substituent on the
 25 isoquinoline ring which is formed when the ring C in the formula (II)
 stands for benzene ring, 5-chloro, 6-chloro, 7-chloro, 7-fluoro, 7-bromo,
 7-methyl, 7-phenyl, 7-hydroxy, 5-methoxy, 6-methoxy, 7-methoxy,
 7-ethoxy, 7-benzyloxy, 7-(4-fluorophenyl)methoxy, 7-(N-methylamino),
 7-(N,N-dimethylamino), 7-methylthio, 7-methylsulfinyl,
 30 7-aminosulfonyloxy, 3-methyl-5-chloro, 4-methyl-6-chloro, 3-methyl-7-
 chloro, 3-methyl-7-fluoro, 3,7-dimethyl, 3-methyl-7-hydroxy,
 4-chloro-7-methoxy, 4-methyl-7-benzyloxy, 3-chloro-7-(4-fluoro-
 phenyl)methoxy, 3-chloro-7-(N-methylamino), 4-chloro-7-(N,N-
 dimethylamino), 3-methyl-7-methoxy, 4-methyl-7-methoxy and
 35 3-chloro-7-methyl can be named.

Where the heterocyclic ring which is formed when the ring C in the formula (II) stands for pyridine ring is 1,6-naphthyridine ring, as substituent on the 1,6-naphthyridine ring, for example, 2-chloro, 3-chloro, 4-chloro, 2-fluoro, 3-fluoro, 2-bromo, 3-bromo, 5 2-iodo, 2-methyl, 3-methyl, 4-methyl, 2-ethyl, 2-n-propyl, 2-sec-butyl, 2,7-dichloro, 2,8-dichloro, 3,7-dichloro, 3,8-dichloro, 4,7-dichloro, 4,8-dichloro, 8-chloro-4-fluoro, 2,7-dimethyl, 2,8-dimethyl, 3,7-dimethyl, 3,8-dimethyl, 4,7-dimethyl, 4,8-dimethyl, 2-methyl-7-ethyl, 2-chloro-7-methyl, 3-chloro-7-methyl, 7-chloro-2-methyl and 10 7-chloro-3-methyl can be named. Of these, 2-chloro, 3-chloro, 3-fluoro, 3-bromo, 3-methyl and 3-chloro-7-methyl are preferred.

Where the heterocyclic ring which is formed when the ring C in the formula (II) stands for pyridine ring is 2,6-naphthyridine ring, as substituent on the 2,6-naphthyridine ring, for example, 15 5-chloro, 7-chloro, 8-chloro, 5-fluoro, 7-fluoro, 5-bromo, 7-bromo, 5-iodo, 5-methyl, 7-methyl, 8-methyl, 5-ethyl, 7-n-propyl, 8-sec-butyl, 3,5-dichloro, 3,7-dichloro, 3,8-dichloro, 4,5-dichloro, 4,7-dichloro, 4,8-dichloro, 4-chloro-8-fluoro, 3,5-dimethyl, 3,7-dimethyl, 3,8-dimethyl, 4,5-dimethyl, 4,7-dimethyl, 4,8-dimethyl, 20 3-chloro-5-methyl, 3-chloro-7-methyl, 3-chloro-8-methyl, 4-chloro-5-methyl, 4-chloro-7-methyl, 4-chloro-8-methyl, 5-chloro-3-methyl, 5-chloro-4-methyl, 7-chloro-3-methyl, 7-chloro-4-methyl, 8-chloro-3-methyl and 8-chloro-4-methyl can be named. Of these, 5-chloro, 7-chloro, 7-fluoro, 7-bromo, 7-methyl and 3,7-dichloro are preferred.

25 Where the heterocyclic ring which is formed when the ring C in the formula (II) stands for pyridine ring is 2,7-naphthyridine ring, as substituent on the 2,7-naphthyridine ring, for example, 5-chloro, 6-chloro, 8-chloro, 5-fluoro, 6-fluoro, 5-bromo, 6-bromo, 5-iodo, 5-methyl, 6-methyl, 8-methyl, 5-ethyl, 6-n-propyl, 8-sec-butyl, 30 3,5-dichloro, 3,6-dichloro, 3,8-dichloro, 4,5-dichloro, 4,6-dichloro, 4,8-dichloro, 4-chloro-8-fluoro, 3,5-dimethyl, 3,6-dimethyl, 3,8-dimethyl, 4,5-dimethyl, 4,6-dimethyl, 4,8-dimethyl, 5-chloro-3-methyl, 5-chloro-4-methyl, 6-chloro-3-methyl, 6-chloro-4-methyl, 8-chloro-3-methyl, 8-chloro-4-methyl, 3-chloro-5-methyl, 3-chloro-6-methyl, 35 3-chloro-8-methyl, 4-chloro-5-methyl, 4-chloro-6-methyl and

4-chloro-8-methyl can be named. Of these, 5-chloro, 6-chloro, 6-fluoro, 6-bromo, 6-methyl, 3,6-dichloro and 3,6-dimethyl are preferred.

Where the heterocyclic ring which is formed when the ring C in the formula (II) stands for pyridine ring is 1,7-naphthyridine ring, as substituent on the 1,7-naphthyridine ring, for example, 2-chloro, 3-chloro, 4-chloro, 2-fluoro, 4-fluoro, 2-bromo, 4-bromo, 4-iodo, 2-methyl, 3-methyl, 4-methyl, 4-ethyl, 3-n-propyl, 2-sec-butyl, 2,5-dichloro, 2,6-dichloro, 3,5-dichloro, 3,6-dichloro, 4,5-dichloro, 4,6-dichloro, 5-chloro-2-fluoro, 2,5-dimethyl, 2,6-dimethyl, 3,5-dimethyl, 3,6-dimethyl, 4,5-dimethyl, 4,6-dimethyl, 2-chloro-5-methyl, 2-chloro-6-methyl, 3-chloro-5-methyl, 3-chloro-6-methyl, 4-chloro-5-methyl, 4-chloro-6-methyl, 5-chloro-2-methyl, 6-chloro-2-methyl, 5-chloro-3-methyl, 6-chloro-3-methyl, 5-chloro-4-methyl and 6-chloro-4-methyl can be named. Of these, 2-chloro, 4-chloro, 2-fluoro, 2-bromo, 2-methyl and 2,6-dichloro are preferred.

Where the heterocyclic ring which is formed when the ring C in the formula (II) stands for furan ring is furo[3,2-c]pyridine, as substituent on the furo[3,2-c]pyridine, besides those named as examples of "substituent on the pyridine ring in the isoquinoline ring where the ring C stands for benzene ring", for example, 2-chloro, 3-chloro, 2-fluoro, 2-bromo, 2-iodo, 2-methyl, 3-methyl, 2-ethyl, 3-n-propyl, 2,6-dichloro, 2,7-dichloro, 3,6-dichloro, 3,7-dichloro, 2,6-dimethyl, 2,7-dimethyl, 3,6-dimethyl, 3,7-dimethyl, 7-chloro-3-fluoro, 2-chloro-6-methyl, 3-chloro-6-methyl, 2-chloro-7-methyl, 3-chloro-7-methyl, 6-chloro-2-methyl, 6-chloro-3-methyl, 7-chloro-2-methyl and 7-chloro-3-methyl can be named. Of these, 2-chloro, 3-chloro, 2-bromo, 2-methyl, 3-methyl, 6-chloro-2-methyl, 6-chloro-3-methyl, 2,6-dimethyl, 3,6-dimethyl and 7-chloro-3-methyl are preferred.

Where the heterocyclic ring which is formed when the ring C in the formula (II) stands for furan ring is furo[3,4-c]pyridine, as substituent on the furo[3,4-c]pyridine, for example, 1-chloro, 3-chloro, 1-fluoro, 1-bromo, 1-iodo, 1-methyl, 3-methyl, 1-ethyl, 3-n-propyl, 1,6-dichloro, 3,6-dichloro, 1,7-dichloro, 3,7-dichloro, 7-chloro-3-fluoro,

1,6-dimethyl, 1,7-dimethyl, 3,6-dimethyl, 3,7-dimethyl,
 1-chloro-6-methyl, 1-chloro-7-methyl, 3-chloro-6-methyl,
 3-chloro-7-methyl, 6-chloro-1-methyl, 6-chloro-3-methyl, 7-chloro-1-
 methyl and 7-chloro-3-methyl can be named. Of these, 1-chloro,
 5 3-chloro, 1-bromo, 1-methyl, 3-methyl, 6-chloro-1-methyl, 3-chloro-6-
 methyl and 6-chloro-3-methyl are preferred.

Where the heterocyclic ring which is formed when the ring
 C in the formula (II) stands for furan ring is furo[2,3-c]pyridine, as
 substituent on the furo[2,3-c]pyridine, for example, 2-chloro, 3-chloro,
 10 3-fluoro, 3-bromo, 3-iodo, 2-methyl, 3-methyl, 3-ethyl, 2-n-propyl,
 2,4-dichloro, 2,5-dichloro, 3,4-dichloro, 3,5-dichloro, 4-chloro-2-fluoro,
 2,4-dimethyl, 2,5-dimethyl, 3,4-dimethyl, 3,5-dimethyl,
 2-chloro-4-methyl, 2-chloro-5-methyl, 3-chloro-4-methyl,
 3-chloro-5-methyl, 4-chloro-2-methyl, 4-chloro-3-methyl, 5-chloro-2-
 15 methyl and 5-chloro-3-methyl can be named. Of these, 2-chloro,
 3-chloro, 3-bromo, 3-methyl, 2-methyl, 2-chloro-5-methyl,
 5-chloro-2-methyl and 5-chloro-3-methyl are preferred.

Where the heterocyclic ring which is formed when the ring
 C in the formula (II) stands for thiophene ring is thieno[3,2-c]-
 20 pyridine, as substituent on the thieno[3,2-c]pyridine, for example,
 2-chloro, 3-chloro, 2-fluoro, 2-bromo, 2-iodo, 2-methyl, 3-methyl,
 2-ethyl, 3-n-propyl, 2,6-dichloro, 2,7-dichloro, 3,6-dichloro,
 3,7-dichloro, 2,6-dimethyl, 2,7-dimethyl, 3,6-dimethyl, 3,7-dimethyl,
 7-chloro-3-fluoro, 2-chloro-6-methyl, 3-chloro-6-methyl,
 25 2-chloro-7-methyl, 3-chloro-7-methyl, 6-chloro-2-methyl,
 6-chloro-3-methyl, 7-chloro-2-methyl and 7-chloro-3-methyl can be
 named. Of these, 2-chloro, 3-chloro, 2-bromo, 2-methyl, 3-methyl,
 6-chloro-2-methyl, 6-chloro-3-methyl, 2,6-dimethyl, 3,6-dimethyl and
 7-chloro-3-methyl are preferred.

Where the heterocyclic ring which is formed when the ring
 C in the formula (II) stands for thiophene ring is thieno[3,4-c]-
 pyridine, as substituent on the thieno[3,4-c]pyridine, for example,
 1-chloro, 3-chloro, 1-fluoro, 1-bromo, 1-iodo, 1-methyl, 3-methyl,
 1-ethyl, 3-n-propyl, 1,6-dichloro, 3,6-dichloro, 1,7-dichloro,
 35 3,7-dichloro, 7-chloro-3-fluoro, 1,6-dimethyl, 1,7-dimethyl,

3,6-dimethyl, 3,7-dimethyl, 1-chloro-6-methyl, 1-chloro-7-methyl, 3-chloro-6-methyl, 3-chloro-7-methyl, 6-chloro-1-methyl, 6-chloro-3-methyl, 7-chloro-1-methyl and 7-chloro-3-methyl can be named. Of these, 1-chloro, 3-chloro, 1-bromo, 1-methyl, 3-methyl, 6-chloro-1-methyl, 3-chloro-6-methyl and 6-chloro-3-methyl are preferred.

Where the heterocyclic ring which is formed when the ring C in the formula (II) stands for thiophene ring is thieno[2,3-c]-pyridine, as substituent on the thieno[2,3-c]pyridine, for example, 2-chloro, 3-chloro, 3-fluoro, 3-bromo, 3-iodo, 2-methyl, 3-methyl, 3-ethyl, 2-n-propyl, 2,4-dichloro, 2,5-dichloro, 3,4-dichloro, 3,5-dichloro, 4-chloro-2-fluoro, 2,4-dimethyl, 2,5-dimethyl, 3,4-dimethyl, 3,5-dimethyl, 2-chloro-4-methyl, 2-chloro-5-methyl, 3-chloro-4-methyl, 3-chloro-5-methyl, 4-chloro-2-methyl, 4-chloro-3-methyl, 5-chloro-2-methyl and 5-chloro-3-methyl can be named. Of these, 2-chloro, 3-chloro, 3-bromo, 3-methyl, 2-methyl, 2-chloro-5-methyl, 5-chloro-2-methyl and 5-chloro-3-methyl are preferred.

As the preferred ring where "R⁹ and R¹⁰ together form the residual members of pyrrolidine ring or piperidine ring (which may be unsubstituted or substituted with a substituent selected from hydroxyl, lower alkoxy and phenyl lower alkoxy)", pyrrolidine ring can be named, and as the substituent on the pyrrolidine ring or piperidine ring, for example, hydroxyl, methoxy, ethoxy, n-propoxy, benzyloxy and (2-phenyl)ethoxy can be named. Of these, hydroxyl, methoxy and benzyloxy are particularly preferred.

In the therapeutic method of IBS of the present invention, "5HT_{1A} agonistic agent", which is useful in the occasion of administering 5-HT_{1A} agonistic agent and 5-HT₃ antagonistic agent simultaneously, in sequence or at an interval, is not subject to any particular limitation, which may be either known compound or novel compound so long as it exhibits 5-HT_{1A} agonistic activity. As a specific example, tandospirone can be named. According to the invention, furthermore, besides those compounds having 5-HT_{1A} agonistic activity alone, those concurrently having pharmacological

activity(ies) other than 5-HT_{1A} agonistic activity can be used as the 5-HT_{1A} agonistic agent.

Again, "5-HT₃ antagonistic agent" to be used in combination with the 5-HT_{1A} agonistic agent in the therapy of IBS following the present invention is not particularly restricted, so long as it exhibits 5-HT₃ antagonistic activity, which may be either known or novel compound. Specifically, for example, alosetron, granisetron, azasetron, tropisetron, ramosetron, ondansetron, lerisetron, cilansetron, itasetron, indisetron, dolasetron and (R)-zacopride can be named. Of these, particularly alosetron and cilansetron are preferred. According to the invention, furthermore, as such 5-HT₃ antagonistic agent, besides those having 5-HT₃ antagonistic activity alone, compounds which concurrently possess pharmacological activity(ies) other than 5-HT₃ antagonistic activity can be similarly used.

The time at which 5-HT_{1A} agonistic agent and 5-HT₃ antagonistic agent manifest their activities in vivo differs according to the kind of active ingredient compounds and form of preparations. Their activity-manifesting time can be readily known by investigating the change in blood concentration or pharmacokinetics after administration of individual medicine. In the therapy following the present invention, it is desirable to administer 5-HT_{1A} agonistic agent and 5-HT₃ antagonistic agent in such a manner that the two activities of 5-HT_{1A} agonistic activity and 5-HT₃ antagonistic activity are substantially simultaneously expressed in vivo. Where a 5-HT_{1A} agonistic agent and 5-HT₃ antagonistic agent whose activity-manifestation time after administration is about the same are used, the two agents can be administered simultaneously or in sequence. Whereas, where a 5-HT_{1A} agonistic agent and 5-HT₃ antagonistic agent having different activity-manifestation time are used, they can be administered at an interval corresponding to the difference, whereby enabling simultaneous manifestation of the two agents' activities in vivo.

In the present invention, a preferred group of compounds

among those represented by the formula (I) are those in which the ring A stands for the group of the formula i) or ii). In particular, the compounds of the formula (I) in which the ring A stands for groups of the formula ii) are more preferable. Furthermore, those of the formula (I) in which the ring A stands for a group of the formula ii) and m is 2 and/or all of R^2 , R^3 and R^4 stand for hydrogen are the most preferred.

Another preferred group of compounds among those represented by the formula (I) of the present invention are those of the formula (I) in which X^1 stands for hydrogen, amino or lower alkyl. Of those, the compounds of the formula (I) in which X^1 stands for amino or lower alkyl are more preferable. In particular, those of the formula (I) in which X^1 stands for amino, methyl or ethyl are the most preferred. Still another preferred group of compounds among those represented by the formula (I) are the compounds of the formula (I) in which X^2 stands for hydrogen.

Another preferred group of compounds among those represented by the formula (I) of the present invention are the compounds of the formula (I) in which Y stands for a direct bond or sulfur atom.

Another preferred group of compounds among those represented by the formula (I) of the present invention are the compounds of the formula (I) in which n stands for 2 or 3.

Still another preferred group of compounds among those represented by the formula (I) of the present invention are the compounds of the formula (I) in which Ar is unsubstituted quinolyl or quinolyl which is substituted with substituent(s) selected from halogen, lower alkyl, hydroxyl, lower alkoxy and phenyl. Of these, the compounds of the formula (I) in which Ar stands for unsubstituted quinolin-2-yl or quinolin-2-yl which is substituted with a substituent selected from halogen, lower alkyl, hydroxyl, lower alkoxy and phenyl are particularly preferred.

In the therapeutic method of IBS provided by the present invention, a group of preferred compounds in the occasions of

administering 5-HT₃ antagonistic agent concurrently having 5-HT_{1A} agonistic activity are the pyrimidine derivatives represented by the formula (I) or pharmaceutically acceptable salts thereof, or the piperazinyipyridine derivatives represented by the formula (II) or pharmaceutically acceptable salts thereof. As those preferred among the pyrimidine derivatives represented by the formula (I) or pharmaceutically acceptable salts thereof, same compounds as specified in the above as "a group of preferred compounds in the present invention" "another preferred group of compounds in the present invention" and "still another preferred group of compounds in the present invention" can be named. Also as those preferred among the piperazinyipyridine derivatives represented by the formula (II) or pharmaceutically acceptable salts thereof, the following compounds can be named:

- 15 7-piperazin-1-ylfuro[2,3-c]pyridine,
- 6-methyl-7-piperazin-1-ylfuro[2,3-c]pyridine,
- 7-(3-methylpiperazin-1-yl)furo[2,3-c]pyridine,
- 7-(4-methylpiperazin-1-yl)furo[2,3-c]pyridine,
- 4-piperazin-1-ylfuro[3,2-c]pyridine,
- 20 4-(3-methylpiperazin-1-yl)furo[3,2-c]pyridine,
- 3-chloro-4-(3-methylpiperazin-1-yl)furo[3,2-c]pyridine,
- 4-(4-methylpiperazin-1-yl)furo[3,2-c]pyridine,
- 4-piperazin-1-ylfuro[3,4-c]pyridine,
- 7-piperazin-1-ylthieno[2,3-c]pyridine,
- 25 7-(3-methylpiperazin-1-yl)thieno[2,3-c]pyridine,
- 3-chloro-7-(3-methylpiperazin-1-yl)thieno[2,3-c]pyridine,
- 7-(4-methylpiperazin-1-yl)thieno[2,3-c]pyridine,
- 4-piperazin-1-ylthieno[3,2-c]pyridine,
- 4-piperazin-1-ylthieno[3,4-c]pyridine,
- 30 4-(3-methylpiperazin-1-yl)thieno[3,2-c]pyridine,
- 6-chloro-4-(3-methylpiperazin-1-yl)thieno[3,2-c]pyridine,
- 4-(4-methylpiperazin-1-yl)thieno[3,2-c]pyridine,
- 2-bromo-4-piperazin-1-ylthieno[3,2-c]pyridine
- dihydrochloride,
- 35 2-bromo-4-(3-methylpiperazin-1-yl)thieno[3,2-c]pyridine,

- 2-bromo-6-methyl-4-(3-methylpiperazin-1-yl)thieno[3,2-c]-pyridine,
 2-bromo-4-(4-methylpiperazin-1-yl)thieno[3,2-c]pyridine,
 2-methyl-4-piperazin-1-ylthieno[3,2-c]pyridine
 5 dihydrochloride,
 2-methyl-4-(3-methylpiperazin-1-yl)thieno[3,2-c]pyridine dihydrochloride,
 2-methyl-4-(4-methylpiperazin-1-yl)thieno[3,2-c]pyridine dihydrochloride,
 10 3-bromo-4-piperazin-1-ylthieno[3,2-c]pyridine dihydrochloride,
 3-bromo-4-(3-methylpiperazin-1-yl)thieno[3,2-c]pyridine,
 3-bromo-4-(4-methylpiperazin-1-yl)thieno[3,2-c]pyridine,
 7-((8aS)-octahydropyrrolo[1,2-a]pyrazin-2-yl)thieno[2,3-c]-
 15 pyridine,
 7-((8aS)-octahydropyrrolo[1,2-a]pyrazin-2-yl)furo[2,3-c]-pyridine,
 2-methyl-4-((8aS)-octahydropyrrolo[1,2-a]pyrazin-2-yl)-thieno[3,2-c]pyridine,
 20 2-methyl-piperazin-1-ylfuro[3,2-c]pyridine,
 7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine,
 4-(4-ethylpiperazin-1-yl)thieno[3,2-c]pyridine,
 5-piperazin-1-yl-1,6-naphthyridine,
 7-chloro-5-piperazin-1-yl-1,6-naphthyridine,
 25 5-(4-ethylpiperazin-1-yl)-1,6-naphthyridine,
 8-piperazin-1-yl-1,7-naphthyridine,
 8-(4-ethylpiperazin-1-yl)-1,7-naphthyridine,
 1-piperazin-1-yl-2,6-naphthyridine,
 1-piperazin-1-yl-2,7-naphthyridine,
 30 3-chloro-1-piperazin-1-ylisoquinoline dihydrochloride,
 3-chloro-7-methoxy-1-piperazin-1-ylisoquinoline,
 3-chloro-1-(4-methylpiperazin-1-yl)isoquinoline dihydrochloride,
 7-methoxy-3-methyl-1-piperazin-1-yl-isoquinoline,
 35 7-methoxy-3,4-dimethyl-1-(4-methylpiperazin-1-yl)-

isoquinoline,

- 7-methoxy-4-methyl-1-piperazin-1-ylisoquinoline,
- 7-methoxy-4-methyl-1-(4-methylpiperazin-1-yl)isoquinoline,
- 7-bromo-1-piperazin-1-ylisoquinoline,
- 5 7-bromo-1-(4-methylpiperazin-1-yl)isoquinoline,
- 7-methoxy-1-(4-methylpiperazin-1-yl)isoquinoline,
- 1-(4-ethylpiperazin-1-yl)-7-methoxyisoquinoline,
- 7-methoxy-1-piperazin-1-ylisoquinoline,
- 1-piperazin-1-ylisoquinoline,
- 10 1-(4-methylpiperazin-1-yl)isoquinoline,
- 1-(4-ethylpiperazin-1-yl)isoquinoline,
- 7-methoxy-1-(3-methylpiperazin-1-yl)isoquinoline,
- 1-(3,5-dimethylpiperazin-1-yl)-7-methoxyisoquinoline,
- 6-methoxy-1-piperazin-1-ylisoquinoline,
- 15 6-methoxy-1-(4-methylpiperazin-1-yl)isoquinoline,
- 1-(4-ethylpiperazin-1-yl)-6-methoxyisoquinoline,
- 5-methoxy-1-piperazin-1-ylisoquinoline,
- 5-methoxy-1-(4-methylpiperazin-1-yl)isoquinoline,
- 1-(4-ethylpiperazin-1-yl)-5-methoxyisoquinoline,
- 20 7-methyl-1-piperazin-1-ylisoquinoline,
- 7-methyl-1-(4-methylpiperazin-1-yl)isoquinoline,
- 1-(4-ethylpiperazin-1-yl)-7-methylisoquinoline,
- 7-chloro-1-piperazin-1-ylisoquinoline,
- 7-chloro-1-(4-methylpiperazin-1-yl)isoquinoline,
- 25 7-chloro-1-(4-ethylpiperazin-1-yl)isoquinoline,
- 7-fluoro-1-(4-methylpiperazin-1-yl)isoquinoline,
- 1-(4-ethylpiperazin-1-yl)-7-fluoroisoquinoline,
- 1-(4-methylpiperazin-1-yl)-7-phenylisoquinoline,
- 1-(4-ethylpiperazin-1-yl)-7-phenylisoquinoline,
- 30 7-phenyl-1-piperazin-1-ylisoquinoline,
- 6-chloro-1-piperazin-1-ylisoquinoline,
- 6-chloro-1-(4-methylpiperazin-1-yl)isoquinoline,
- 6-chloro-1-(4-ethylpiperazin-1-yl)isoquinoline,
- 5-chloro-1-piperazin-1-ylisoquinoline,
- 35 5-chloro-1-(4-methylpiperazin-1-yl)isoquinoline,

- 5-chloro-1-(4-ethylpiperazin-1-yl)isoquinoline,
 7-fluoro-1-piperazin-1-ylisoquinoline,
 7-chloro-1-[4-[4-(3-methoxyphenyl)butyl]piperazin-1-yl]-
 isoquinoline,
 5 7-methoxy-1-[4-[4-(3-methoxyphenyl)butyl]piperazin-1-yl]-
 isoquinoline,
 7-chloro-1-[4-[trans-4-(3-methoxyphenyl)cyclohexan-1-yl]-
 piperazin-1-yl]isoquinoline,
 7-methoxy-1-[4-[trans-4-(3-methoxyphenyl)cyclohexan-1-yl]-
 10 piperazin-1-yl]isoquinoline,
 1-((8aS)-octahydropyrrolo[1,2-a]pyrazin-2-yl)-7-
 methoxyisoquinoline,
 7-chloro-1-((8aS)-octahydropyrrolo[1,2-a]pyrazin-2-yl)-
 isoquinoline,
 15 8-((8aS)-octahydropyrrolo[1,2-a]pyrazin-2-yl)-1,7-
 naphthyridine,
 5-((8aS)-octahydropyrrolo[1,2-a]pyrazin-2-yl)-1,6-
 naphthyridine,
 7-chloro-1-((8aR)-octahydropyrrolo[1,2-a]pyrazin-2-yl)-
 20 isoquinoline,
 1-((8aR)-octahydropyrrolo[1,2-a]pyrazin-2-yl)-7-
 methoxyisoquinoline,
 3-chloro-1-((8aS)-octahydropyrrolo[1,2-a]pyrazin-2-yl)-
 isoquinoline,
 25 3-chloro-1-((8aS)-octahydropyrrolo[1,2-a]pyrazin-2-yl)-7-
 methylisoquinoline,
 7-chloro-1-octahydropyrido[1,2-a]pyrazin-2-ylisoquinoline,
 7-methoxy-1-octahydropyrido[1,2-a]pyrazin-2-ylisoquinoline,
 7-methylthio-1-(S)-octahydropyrido[1,2-a]pyran-2-
 30 ylisoquinoline,
 7-methylsulfinyl-1-(S)-octahydropyrido[1,2-a]pyran-2-
 ylisoquinoline,
 7-hydroxy-1-octahydropyrido[1,2-a]pyrazin-2-ylisoquinoline,
 1-(S)-octahydropyrido[1,2-a]pyran-2-yl-7-hydroxy-
 35 isoquinoline,

1-octahydropyrido[1,2-a]pyrazin-2-yl-7-sulfamoyloxy-
isoquinoline,

1-(S)-octahydropyrido[1,2-a]pyran-2-yl-7-sulfamoyloxy-
isoquinoline,

- 5 1-(4-benzylpiperazin-1-yl)-7-chloroisoquinoline,
 1-(4-benzylpiperazin-1-yl)-7-dimethylaminoisoquinoline,
 7-methylamino-1-piperazin-1-ylisoquinoline,
 7-ethylamino-1-piperazin-1-ylisoquinoline,
 7-dimethylamino-1-piperazin-1-ylisoquinoline,
10 7-dimethylamino-1-(4-methylpiperazin-1-yl)isoquinoline,
 7-methylamino-1-(4-methylpiperazin-1-yl)isoquinoline,
 1-[4-(4-fluorobenzyl)piperazin-1-yl]-7-methoxyisoquinoline,
 1-[4-(4-fluorobenzyl)piperazin-1-yl]isoquinoline,
 7-hydroxy-1-piperazin-1-ylisoquinoline hydrochloride,
15 7-hydroxy-1-(4-methylpiperazin-1-yl)isoquinoline,
 7-ethoxy-1-piperazin-1-ylisoquinoline,
 7-(4-fluorobenzyloxy)-1-piperazin-1-ylisoquinoline,
 7-benzyloxy-1-piperazin-1-ylisoquinoline,

and

- 20 7-sulfamoyloxy-1-piperazin-1-ylisoquinoline hydrochloride.

Of these, particularly the following compounds are
preferred:

- 7-chloro-1-(4-methylpiperazin-1-yl)isoquinoline,
 7-((8aS)-octahydropyrrolo[1,2-a]pyrazin-2-yl)thieno[2,3-c]-
25 pyridine,
 7-((8aS)-octahydropyrrolo[1,2-a]pyrazin-2-yl)furo[2,3-c]-
pyridine,
 2-methyl-4-((8aS)-octahydropyrrolo[1,2-a]pyrazin-2-yl)-
thieno[3,2-c]pyridine,
30 7-methoxy-1-((8aR)-octahydropyrrolo[1,2-a]pyrazin-2-yl)-
isoquinoline,

and

2-bromo-4-(4-methylpiperazin-1-yl)thieno[3,2-c]pyridine.

- In the therapeutic method provided by the present
35 invention, wherein 5-HT_{1A} agonistic agent and 5-HT₃ antagonistic

agent are administered simultaneously, in sequence or at an interval, preferred 5-HT_{1A} agonistic agent is tandospirone, and preferred 5-HT₃ antagonistic agents are alosetron, granisetron, azasetron, tropisetron, ramosetron, ondansetron, lerisetron, cilansetron, itasetron, indisetron, dolasetron and (R)-zacopride. Of these, particularly preferred 5-HT₃ antagonistic agents are alosetron and cilansetron.

As representative examples of the compounds of the formula (I) which are provided by the present invention, besides those in the later appearing Examples, the following can be named:

- 3-amino-6-benzyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-5,6,7,8-tetrahydro-3H-pyrido[4,3-d]pyrimidin-4-one,
- 3-amino-6-benzyl-8-methyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-5,6,7,8-tetrahydro-3H-pyrido[4,3-d]pyrimidin-4-one,
- 3-amino-6-benzoyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-5,6,7,8-tetrahydro-3H-pyrido[4,3-d]pyrimidin-4-one,
- 3-amino-6-methyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-5,6,7,8-tetrahydro-3H-pyrido[4,3-d]pyrimidin-4-one,
- 3-amino-7-benzyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-5,6,7,8-tetrahydro-3H-pyrido[3,4-d]pyrimidin-4-one,
- 3-amino-7-methyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-5,6,7,8-tetrahydro-3H-pyrido[3,4-d]pyrimidin-4-one,
- 3-amino-5-chloro-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-5,6,7,8-tetrahydro-3H-quinazolin-4-one,
- 3-amino-6-chloro-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-5,6,7,8-tetrahydro-3H-quinazolin-4-one,
- 3-amino-7-chloro-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-5,6,7,8-tetrahydro-3H-quinazolin-4-one,
- 3-amino-8-chloro-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-5,6,7,8-tetrahydro-3H-quinazolin-4-one,
- 3-amino-6-fluoro-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-5,6,7,8-tetrahydro-3H-quinazolin-4-one,
- 3-amino-7-fluoro-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-

- 5,6,7,8-tetrahydro-3H-quinazolin-4-one,
 3-amino-6-bromo-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-
 5,6,7,8-tetrahydro-3H-quinazolin-4-one,
 3-amino-7-bromo-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-
 5 5,6,7,8-tetrahydro-3H-quinazolin-4-one,
 3-amino-5-methoxy-2-[4-(4-quinolin-2-ylpiperazin-1-yl)-
 butyl]-5,6,7,8-tetrahydro-3H-quinazolin-4-one,
 3-amino-6-methoxy-2-[4-(4-quinolin-2-ylpiperazin-1-yl)-
 butyl]-5,6,7,8-tetrahydro-3H-quinazolin-4-one,
 10 3-amino-6-cyclohexyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)-
 butyl]-5,6,7,8-tetrahydro-3H-quinazolin-4-one,
 3-amino-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-7-
 trifluoromethyl-5,6,7,8-tetrahydro-3H-quinazolin-4-one,
 3-amino-6-benzyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-
 15 5,6,7,8-tetrahydro-3H-quinazolin-4-one,
 3-amino-6-phenethyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)-
 butyl]-5,6,7,8-tetrahydro-3H-quinazolin-4-one,
 3-amino-6-propyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-
 5,6,7,8-tetrahydro-3H-quinazolin-4-one,
 20 3-amino-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-7,8-
 dihydro-3H,6H-thiopyrano[3,2-d]pyrimidin-4-one,
 3-amino-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-7,8-
 dihydro-3H,5H-thiopyrano[4,3-d]pyrimidin-4-one,
 3-amino-6,6-dioxo-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-
 25 7,8-dihydro-3H,5H-thiopyrano[4,3-d]pyridine-4-one,
 3-amino-6-oxo-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-7,8-
 dihydro-3H,5H-thiopyrano[4,3-d]pyridine-4-one,
 3-amino-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-5,8-
 dihydro-3H,6H-thiopyrano[3,4-d]pyrimidin-4-one,
 30 3-amino-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-7,8-
 dihydro-3H,5H-pyrano[4,3-d]pyrimidin-4-one,
 3-amino-4-oxo-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-
 3,4,5,6,7,8-hexahydroquinazolinone-6-carboxylic acid,
 ethyl 3-amino-4-oxo-2-[4-(4-quinolin-2-ylpiperazin-1-yl)-
 35 butyl]-3,4,5,6,7,8-hexahydroquinazolinone-6-carboxylate,

- 3-amino-4-oxo-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-
3,4,5,6,7,8-hexahydroquinazolinone-6-carbonitrile,
3-amino-4-oxo-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-
3,4,5,6,7,8-hexahydroquinazolinone-7-carbonitrile,
5 3,6-diamino-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-
5,6,7,8-tetrahydro-3H-quinazolin-4-one,
3-amino-6-methylamino-2-[4-(4-quinolin-2-ylpiperazin-1-yl)-
butyl]-5,6,7,8-tetrahydro-3H-quinazolin-4-one,
3-amino-6,6-dimethylamino-2-[4-(4-quinolin-2-ylpiperazin-
10 1-yl)butyl]-5,6,7,8-tetrahydro-3H-quinazolin-4-one,
3-amino-6-nitro-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-
5,6,7,8-tetrahydro-3H-quinazolin-4-one,
3-amino-6-methyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-
5,6-dihydro-3H,7H-cyclopenta[d]pyrimidin-4-one,
15 3-amino-6-chloro-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-
5,6-dihydro-3H,7H-cyclopenta[d]pyrimidin-4-one,
3-amino-6-hydroxy-2-[4-(4-quinolin-2-ylpiperazin-1-yl)-
butyl]-5,6-dihydro-3H,7H-cyclopenta[d]pyrimidin-4-one,
3-amino-5-methyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-
20 5,6-dihydro-3H,7H-cyclopenta[d]pyrimidin-4-one,
3-amino-6-methyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-
5,6,7,8-tetrahydro-3H,9H-cyclohepta[d]pyrimidin-4-one,
3-amino-6-phenyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-
5,6-dihydro-3H,7H-cyclopenta[d]pyrimidin-4-one,
25 3-amino-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3H,7H-
pyrrolo[2,3-d]pyrimidin-4-one,
3-amino-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3H,5H-
pyrrolo[3,2-d]pyrimidin-4-one,
3-amino-6-methyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-
30 3H,5H-pyrrolo[3,2-d]pyrimidin-4-one,
3-amino-6-ethyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-
3H,5H-pyrrolo[3,2-d]pyrimidin-4-one,
3-amino-6,7-dimethyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)-
butyl]-3H,5H-pyrrolo[3,2-d]pyrimidin-4-one,
35 3,5-dimethyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-

- 5,6,7,8-tetrahydro-3H-quinazolin-4-one,
 3,7-dimethyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-
 5,6,7,8-tetrahydro-3H-quinazolin-4-one,
 3,8-dimethyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-
 5 5,6,7,8-tetrahydro-3H-quinazolin-4-one,
 3-methyl-2-[4-[4-(5-methylquinolin-2-yl)piperazin-1-yl]-
 butyl]-5,6,7,8-tetrahydro-3H-quinazolin-4-one,
 3-methyl-2-[4-[4-(6-methylquinolin-2-yl)piperazin-1-yl]-
 butyl]-5,6,7,8-tetrahydro-3H-quinazolin-4-one,
 10 3-methyl-2-[4-[4-(7-methylquinolin-2-yl)piperazin-1-yl]-
 butyl]-5,6,7,8-tetrahydro-3H-quinazolin-4-one,
 2-[4-[4-(6-bromoquinolin-2-yl)piperazin-1-yl]butyl]-3-
 methyl-5,6,7,8-tetrahydro-3H-quinazolin-4-one,
 2-[4-[4-(6-chloroquinolin-2-yl)piperazin-1-yl]butyl]-3-
 15 methyl-5,6,7,8-tetrahydro-3H-quinazolin-4-one,
 2-[4-[4-(6-hydroxyquinolin-2-yl)piperazin-1-yl]butyl]-3-
 methyl-5,6,7,8-tetrahydro-3H-quinazolin-4-one,
 2-[4-[4-(3-hydroxyquinolin-2-yl)piperazin-1-yl]butyl]-3-
 methyl-5,6,7,8-tetrahydro-3H-quinazolin-4-one,
 20 6-methoxy-3-methyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)-
 butyl]-3H-quinazolin-4-one,
 6-methoxy-3-methyl-2-[4-[4-(4-methylquinolin-2-yl)-
 piperazin-1-yl]butyl]-3H-quinazolin-4-one,
 2-[4-[4-(4-chloroquinolin-2-yl)piperazin-1-yl]butyl]-6-
 25 methoxy-3-methyl-3H-quinazolin-4-one,
 3-ethyl-6-methoxy-2-[4-(4-quinolin-2-ylpiperazin-1-yl)-
 butyl]-3H-quinazolin-4-one,
 3,6-dimethyl-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylthio]-
 5,6,7,8-tetrahydro-3H-quinazolin-4-one,
 30 3-ethyl-6-methyl-2-[3-(4-quinolin-2-ylpiperazin-1-yl)-
 propylthio]-5,6,7,8-tetrahydro-3H-quinazolin-4-one,
 3-ethyl-6-methyl-2-[3-[4-(5-methylquinolin-2-yl)piperazin-1-
 yl]propylthio]-5,6,7,8-tetrahydro-3H-quinazolin-4-one,
 2-[3-[4-(4-chloroquinolin-2-yl)piperazin-1-yl]propylthio]-3,6-
 35 dimethyl-5,6,7,8-tetrahydro-3H-quinazolin-4-one,

- 3,6-dimethyl-2-[3-[4-(4-methylquinolin-2-yl)piperazin-1-yl]-butylthio]-5,6,7,8-tetrahydro-3H-quinazolin-4-one,
 3,6-dimethyl-2-[3-(4-quinolin-2-yl)propylamino]-5,6,7,8-tetrahydro-3H-quinazolin-4-one,
 5 3,6-dimethyl-2-[3-(4-quinolin-2-yl)piperazin-1-yl]-butylamino]-5,6,7,8-tetrahydro-3H-quinazolin-4-one,
 2-[3-[4-(4-chloroquinolin-2-yl)piperazin-1-yl]butylamino]-3,6-dimethyl-5,6,7,8-tetrahydro-3H-quinazolin-4-one,
 3,6-dimethyl-2-[4-(4-quinolin-2-yl)piperazin-1-yl]butyl]-
 10 3H-quinazolin-4-one,
 2-[4-[4-(4-chloroquinolin-2-yl)piperazin-1-yl]butyl]-3-ethyl-6-methyl-3H-quinazolin-4-one,
 3-methyl-2-[4-(4-quinolin-2-yl)piperazin-1-yl]pentyl]-3H-quinazolin-4-one,
 15 6-methoxy-3-methyl-2-[3-(4-quinolin-2-yl)piperazin-1-yl]-propylthio]-3H-quinazolin-4-one,
 3-ethyl-6-methoxy-2-[3-(4-quinolin-2-yl)piperazin-1-yl]-butylthio]-3H-quinazolin-4-one,
 3-benzyl-2-[3-(4-quinolin-2-yl)piperazin-1-yl]-
 20 butylamino]-3H-quinazolin-4-one,
 6,7-dichloro-3-methyl-2-[3-(4-quinolin-2-yl)piperazin-1-yl]-butylamino]-3H-quinazolin-4-one,
 3,5,6-trimethyl-2-[3-(4-quinolin-2-yl)piperazin-1-yl]-butylamino]-3H-thieno[2,3-d]pyrimidin-4-one,
 25 3-ethyl-5,6-dimethyl-2-[3-[4-(4-methylquinolin-2-yl)piperazin-1-yl]butylthio]-3H-thieno[2,3-d]pyrimidin-4-one,
 2-[4-(4-benzothiazol-2-yl)piperazin-1-yl]pentyl]-3-methyl-5,6,7,8-tetrahydro-3H-quinazolin-4-one,
 2-[4-(4-benzothiazol-2-yl)piperazin-1-yl]pentyl]-3-ethyl-6-
 30 methyl-5,6,7,8-tetrahydro-3H-quinazolin-4-one,
 2-[3-(4-benzothiazol-2-yl)piperazin-1-yl]butylthio]-3-ethyl-5,6,7,8-tetrahydro-3H-quinazolin-4-one,
 2-[4-(4-benzothiazol-2-yl)piperazin-1-yl]butyl]-6-chloro-3-methyl-3H-quinazolin-4-one,
 35 and

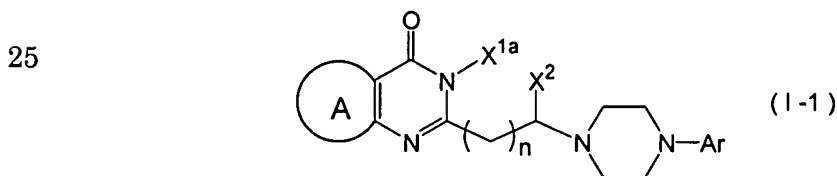
2-[3-(4-benzothiazol-2-ylpiperazin-1-yl)butylthio]-3-methyl-3H-quinazolin-4-one.

Those compounds of the formula (I) provided by the present invention and those that are used in therapy of IBS following the present invention can also be present in the form of salts when occasions demand. As such salts, for example, those with inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like; and those with organic acid such as acetic acid, oxalic acid, citric acid, lactic acid, tartaric acid, p-toluenesulfonic acid and the like can be named. Of those, pharmaceutically acceptable salts are preferred.

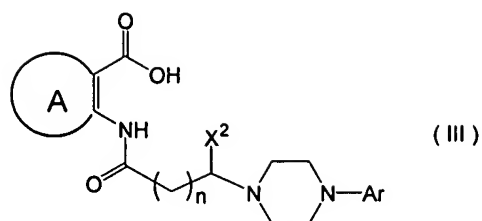
According to the present invention, those compounds of the formula (I) can be prepared by, for example, any of the methods as described in the following (a) – (e), depending on the kind of X^1 and Y.

Method (a):

Compounds of the formula (I) wherein X^1 stands for amino, lower alkyl, phenyl lower alkyl or substituted or unsubstituted phenyl and Y is direct bond, i.e., the pyrimidine derivatives represented by the following formula,



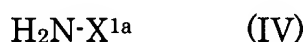
in the formula, ring A, n, X^2 and Ar have the previously given significations, and X^{1a} stands for amino, lower alkyl, phenyl lower alkyl or substituted or unsubstituted phenyl, can be prepared by, for example, treating a compound of the formula,



5

in the formula, ring A, n, X² and Ar have the previously
 given significations,
 with acetic anhydride, and successively reacting the reaction product
 with a compound of the formula,

10



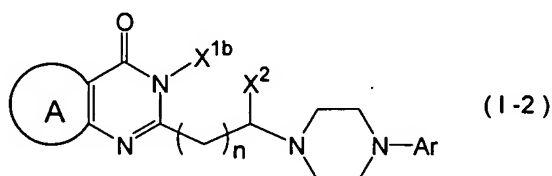
in which X^{1a} has the previously given signification,
 without intervening isolation of the reaction product.

15

Method (b):

Compounds of the formula (I) wherein X¹ stands for lower
 alkylamino, di-lower alkylamino or lower alkylideneamino and Y is
 direct bond, i.e., the pyrimidine derivatives represented by the
 following formula,

20



25

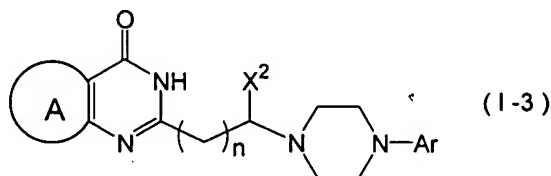
in which ring A, n, X² and Ar have the previously given
 significations and X^{1b} stands for lower alkylamino, di-lower
 alkylamino or lower alkylideneamino,
 can be prepared by, for example, either N-alkylating, N,N-
 dialkylating or N-alkylidenating the compounds of the formula (I-1)
 wherein X^{1a} stands for amino, as obtained by the method (a); or
 further N-alkylating the compounds of the formula (I-2) wherein X^{1b}
 stands for lower alkylamino.

30

35 Method (c):

Compounds of the formula (I) wherein X^1 stands for hydrogen and Y is direct bond, i.e., the pyrimidine derivatives of the following formula,

5



10

in which ring A, n, X^2 and Ar have the previously given significations,

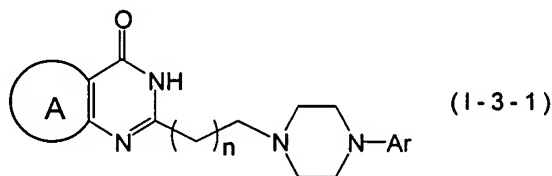
can be prepared by, for example, treating the compounds of the formula (I-1) wherein X^{1a} stands for amino, as obtained by the method (a), with sodium nitrite.

15

Alternative method (c-1):

The compounds of the formula (I-3) in which X^2 stands for hydrogen, in the above method (c), i.e., the pyrimidine derivatives of the following formula,

20

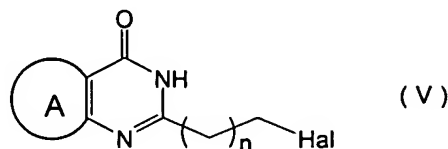


25

in which ring A, n and Ar have the previously given significations,

may also be prepared by reacting a compound of the formula,

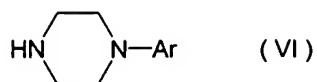
30



in which ring A and n have the previously given significations, and Hal stands for halogen,

35

with a compound of a formula,

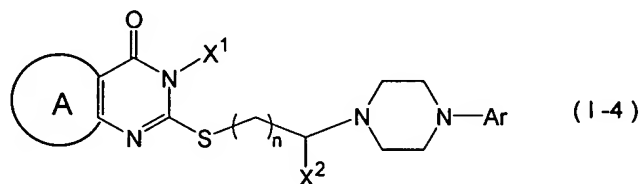


5

in which Ar has the previously given signification.

Method (d):

The compound of the formula (I) in which Y stands for
10 sulfur, i.e., the pyrimidine derivatives of the following formula,

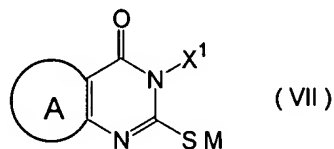


15

in which ring A, X¹, n, X² and Ar have the previously given
significations,

can be prepared by, for example, reacting a compound of a formula

20



25

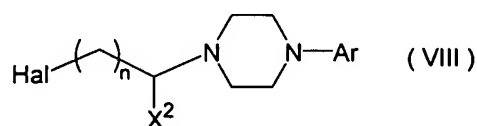
in which ring A and X¹ have the previously given
significations,

M stands for alkali metal or alkaline earth metal, and

SM means that the sulfur atom is in the form of a salt of
the metal,

with a compound of the formula,

30



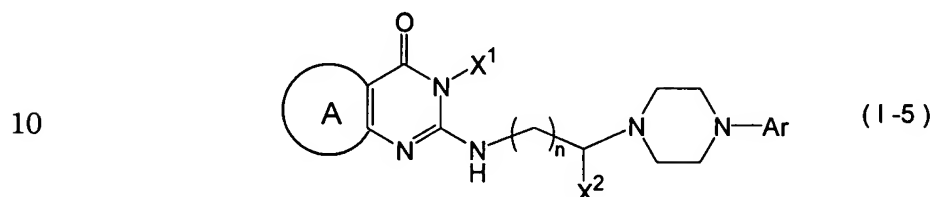
35

in which n, X², Ar and Hal have the previously given

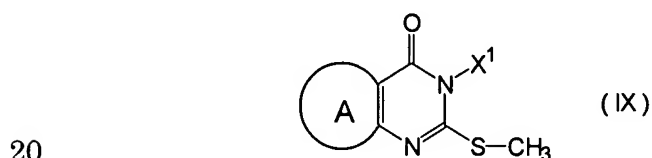
significations.

Method (e):

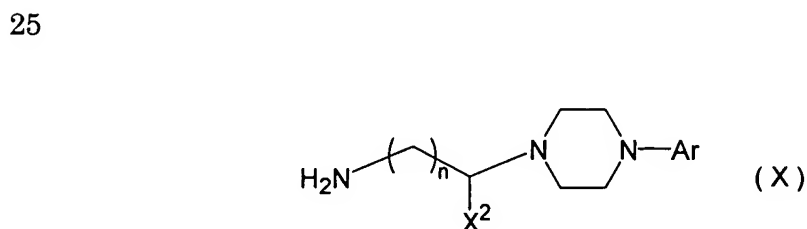
The compounds of the formula (I) in which Y stands for
 5 nitrogen atom, i.e., the pyrimidine derivatives of the following
 formula,



in which ring A, X¹, n, X² and Ar have the previously given
 significations,
 15 can be prepared by, for example, reacting a compound of the formula,



in which ring A and X¹ have the previously given
 significations,
 with a compound of the formula,



30 in which n, X² and Ar have the previously given
 significations.

The treatment with acetic anhydride of a compound of the
 formula (III) in the above method (a) can be conducted using
 35 generally about 1 – 10 mols, preferably about 1.3 – 5 mols, of acetic

anhydride per mol of the compound of the formula (III), in an inert organic solvent such as amides, e.g., N,N-dimethylformamide, N,N-dimethylacetamide and the like; alcohols, e.g., methanol, ethanol, isopropanol and the like; or ethers, e.g., tetrahydrofuran, dioxane and the like; at 0°C – reflux temperature of the reaction mixture, preferably room temperature – reflux temperature of the reaction mixture.

Then adding a compound of the formula (IV) to the reaction mixture to carry out the reaction at 0°C – reflux temperature of the reaction mixture, the object compound of the formula (I-1) can be obtained.

The use rate of the compound of the formula (IV) to that of the formula (III) is not particularly limited. Whereas, in general terms it is preferred to use the compound of the formula (IV) within a range of the mol number of the residual acetic anhydride, i.e., the remaining mol number after subtracting the mol number of the formula (III) compound from that of the used acetic anhydride, plus at least 1 mol, preferably 1.2 – 10 mols, inter alia, 1.3 – 5 mols, per mol of the formula (III) compound.

N-alkylation reaction of the formula (I-1) compound in the above method (b) can be carried out by nucleophilic substitution reaction using alkyl halide or the like, or by reductive alkylation reaction using aldehydes or the like; and the N-alkylidenation reaction can be conducted by dehydration reaction using aldehydes or the like. Those reactions can be generally conducted in inert organic solvent such as amides, e.g., N,N-dimethylformamide, N,N-dimethylacetamide and the like; alcohols, e.g., methanol, ethanol, isopropanol and the like; or ethers, e.g., tetrahydrofuran, dioxane and the like; at 0°C – reflux temperature of the reaction mixture, preferably room temperature – reflux temperature of the reaction mixture.

The use rate of alkylation agent or alkylidenation agent such as alkyl halides or aldehydes used for N-alkylation or N-alkylidenation of compounds of the formula (I-1) is not particularly limited. In general terms, in case of leading a formula (I-1) compound whose X^{1a} stands for amino to a formula (I-2) compound

whose X^{1b} stands for lower alkylamino or lower alkylideneamino, or of leading a formula (I-2) compound whose X^{1b} stands for lower alkylamino to another formula (I-2) compound whose X^{1b} stands for di-lower alkylamino (in which the lower alkyl groups may be same or different), either of the agents can be used within a range of at least 1 mol, preferably 1.2 – 10 mols, inter alia, 1.3 – 5 mols, per mol of the formula (I-1) compound whose X^{1a} stands for amino or of the formula (I-2) compound whose X^{1b} stands for lower alkylamino. Again, in case of leading a formula (I-1) compound whose X^{1a} stands for amino to a formula (I-2) compound whose X^{1b} stands for di-lower alkylamino in which the lower alkyl groups are the same, the agent can be used within a range of at least 2 mols, preferably 2.2 – 10 mols, inter alia, 3 – 5 mols, per mol of the formula (I-1) compound whose X^{1a} stands for amino.

The reaction in the above method (c) of treating a formula (I-1) compound whose X^{1a} stands for amino with sodium nitrite can generally be conducted in mixed solvent of acetic acid and water, at 0°C – reflux temperature of the reaction mixture, preferably room temperature – reflux temperature of the reaction mixture.

The use rate of sodium nitrite to the formula (I-1) compound whose X^{1a} stands for amino is not particularly limited, while generally it can be at least 1 mol, preferably 1.5 – 10 mols, inter alia, 2 – 5 mols, of sodium nitrite per mol of the formula (I-1) compound whose X^{1a} stands for amino.

The reaction of a formula (V) compound with a formula (VI) compound in the alternative method (c-1) can be generally conducted in an inert organic solvent such as amides, e.g., N,N-dimethylformamide, N,N-dimethylacetamide and the like; alcohols, e.g., methanol, ethanol, isopropanol and the like; ethers, e.g., tetrahydrofuran, dioxane and the like; ketones, e.g., acetone, diethyl ketone; or aromatic hydrocarbon, e.g., benzene, toluene; and where necessary, in the presence of alkalis such as sodium hydride, sodium methoxide, potassium butoxide, potassium carbonate, potassium hydroxide and the like or organic base such as triethylamine, 2,6-di-tert-butyl-4-methylpyridine and the like, at temperatures

ranging -20°C – reflux temperature of the reaction mixture, preferably 0°C – 60°C .

The use rate of the formula (VI) compound to the formula (V) compound is not particularly limited. Generally, the formula (VI) compound can be used in the range of at least 1 mol, preferably 1.05 – 4 mols, inter alia, 1.2 – 2 mols, per mol of the formula (V) compound.

The reaction of a formula (VII) compound with a formula (VIII) compound in the above method (d) can be generally conducted in an inert organic solvent such as amides, e.g., N,N-dimethylformamide, N,N-dimethylacetamide and the like; alcohols, e.g., methanol, ethanol, isopropanol and the like; ethers, e.g., tetrahydrofuran, dioxane and the like; or organic base, e.g., pyridine and the like; where necessary in the presence of alkalis such as sodium hydride, sodium methoxide, potassium butoxide, potassium carbonate, potassium hydroxide and the like or organic base such as triethylamine, 2,6-di-tert-butyl-4-methylpyridine and the like, at temperatures ranging -20°C – reflux temperature of the reaction mixture, preferably 0°C – 60°C .

The use rate of the formula (VIII) compound to the formula (VII) compound is not particularly limited. Generally, the formula (VIII) compound can be used in the range of at least 1 mol, preferably 1.1 – 5 mols, inter alia, 1.2 – 2 mols, per mol of the formula (VII) compound. Also it is adequate to use 1.2 – 10 mols of the alkalis or organic bases per mol of the formula (VII) compound.

The reaction of a formula (IX) compound with a formula (X) compound in the above method (e) can be generally conducted by heating them in pyridine to the reflux temperature of the reaction mixture.

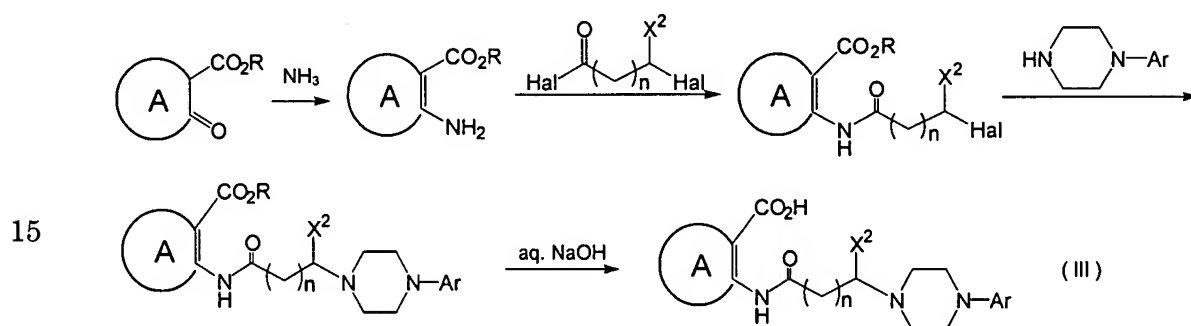
The use rate of the formula (X) compound to the formula (IX) compound is not particularly limited. In general terms, at least 1 mol, preferably 1.1 – 5 mols, inter alia, 1.2 – 2 mols of the formula (X) compound can be used per mol of the formula (IX) compound.

Thus, compound of the above formulae (I-1), (I-2), (I-3), (I-4) or (I-5), i.e., compounds of the formula (I) intended by the present

invention, can be prepared.

The compounds of the formula (III) which are used as the starting material in the above method (a) can be readily synthesized by following per se known method of synthesis, for example, by following the route as illustrated in the following reaction scheme 1. Concerning the particulars about the reaction scheme 1 such as reaction conditions, Steps 7-1-A to D in later appearing Example 7-1 are to be referred to.

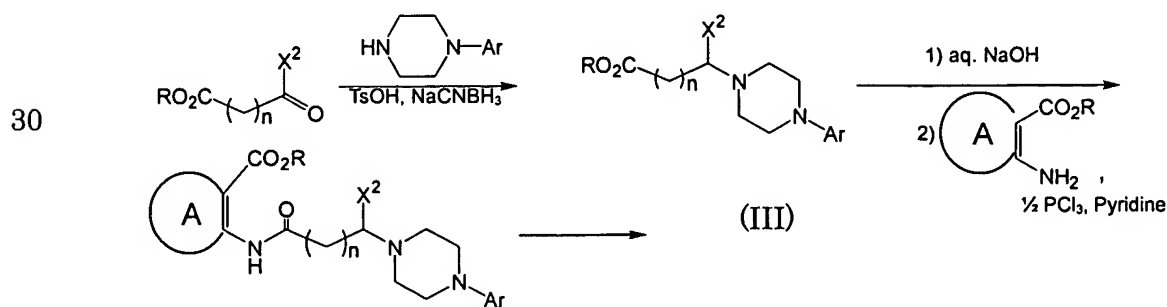
Reaction scheme 1:



in the above formulae, ring A, n, X², Ar, Hal and R have the previously given significations, and R stands for lower alkyl.

Compounds of the formula (III) which are used as the starting material in the above method (a) can also be synthesized by the following the route illustrated in reaction scheme 2. Concerning the particulars of the reaction scheme 2 such as the reaction conditions, later appearing Examples 7 – 14 are to be referred to.

Reaction scheme 2:



in the above formulae, ring A, n, X², Ar and R have the previously given significations.

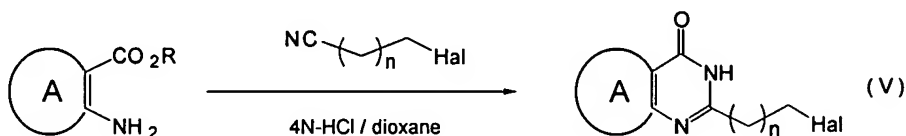
Compounds of the formula (V) which are used as the starting material in the alternative method (c-1) can be synthesized by

5 following per se known methods of synthesis, for example, through the route as illustrated in the following reaction scheme 3.

Concerning further particulars of the reaction scheme 3 such as the reaction conditions, Step 3-1-A in later appearing Example 3-1 is to be referred to.

10

Reaction scheme 3:



15

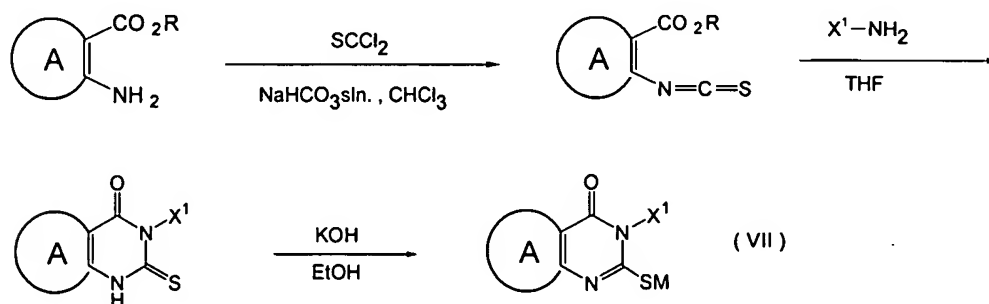
in the above formulae, ring A, n, Hal and R have the previously given significations.

Compounds of the formula (VII) which are used as the starting material in the above method (d) can be synthesized in accordance with per se known synthesis methods, for example, following the method as described in J. Med. Chem., 40, 574-585 (1997), via the route as illustrated by the following reaction scheme 4.

20

Reaction scheme 4:

25



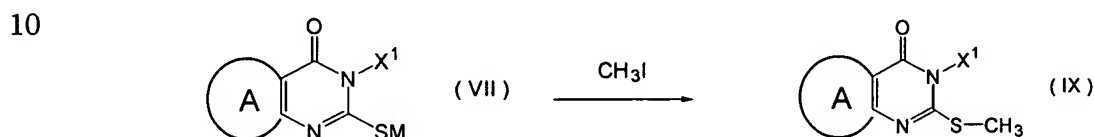
30

in the above formulae, ring A, X¹, R and M have the previously given significations.

35

Compounds of the formula (IX) which are used as the starting material in the above method (e) can be synthesized by, for example, methylating compounds of the formula (VII) via a route as illustrated in the following reaction scheme 5. Concerning the
 5 particulars of the reaction scheme such as the reaction conditions, Step 7-29-A in the later appearing Example 7-29 is to be referred to.

Reaction scheme 5:



15 in the above formulae, ring A, X¹ and M have the previously given significations.

Those compounds of the formula (I) of the present invention which are prepared by above-described methods can be isolated from the reaction mixtures and purified by the means known per se, for example, recrystallization, column chromatography, preparative
 20 chromatography and the like.

Again, while most of the compounds of the formula II which are used in therapy of IBS following the present invention are known from literature (e.g., J. Med. Chem., 42, 4362 – 4379 (1999)), even when they are novel compounds, they can be readily synthesized by
 25 synthesis methods disclosed in literature references or by following later given production examples.

The pyrimidine derivatives of the formula (I) of the present invention or their pharmaceutically acceptable salts concurrently
 30 possess 5-HT_{1A} agonistic activity and 5-HT₃ antagonistic activity, and are effective for treatment and therapy of diseases associated with 5HT_{1A} and/or 5HT₃ receptors in human beings and other mammals, for example, IBS, functional dyspepsia (FD), anxiety, urinary incontinence, anischuria, depression, prostate cancer, asyndesis,
 35 pollakiuria, schizophrenia, overactive bladder syndrome, psychosis,

lower urinary tract symptom, senile dementia, bladder outlet obstruction associated with benign prostatic hyperplasia, Alzheimer disease, interstitial cystitis, addiction/withdrawal symptom, chronic prostatitis, cognitive impairment, acute ischemic stroke,

5 Huntington's disease, transient ischemic attack, Parkinson's disease, head or spinal cord trauma, amyotrophic lateral sclerosis, fetal hypoxemia, AIDS dementia complex, nonulcer dyspepsia, chronic neurodegenerative disease, for example, retinal disease, reflux esophagitis, alcohol or cocaine addiction, hypersensitive bowel

10 syndrome, extrapyramidal disorder, apnea/hypopnea syndrome, panic disorder, tremor, disturbance of short-term memory, nausea or emesis, alcoholism, epilepsy, nicotine dependence, sleep disorder, drug addiction, pain, eating disorder, sexual dysfunction, posttraumatic stress disorder, obesity, autism, cough, nerve root compression

15 syndrome, myofascial syndrome, neuropathy, tendomyosis, algetic dystrophy, tendinosis, agitation, tendopathy, hostility, synovial bursa related disease, obsessive-compulsive disorder, periarthropathy, cognition enhancement, myofascial pain syndrome, premenstrual tension syndrome, autonomic imbalance, essential hypertension,

20 psychophysiologic disorder, convulsion, peptic ulcer, mania, gastritis, migraine, meniscal lesion, polyarthritis, traumatic arthritis, paraneoplastic syndrome, osteochondritis dissecans, tumor-elicited inflammatory disease, osteonecrosis, inflammatory exudation, articularis chondromatosis, connective tissue disease, chronic

25 obstructive pulmonary disease (COPD), infectious arthritis, acute respiratory distress syndrome (ARDS), seronegative spondyloarthropathy, bronchitis, vasculitis, pneumoconiosis, sarcoid arthropathy, laryngospasm, pulmonary angiitis, pulmonary granuloma, extrinsic allergic alveolitis, chronic fatigue syndrome,

30 contact hypersensitivity, glaucoma, and so on. In particular, they are very useful for therapy and treatment of the diseases on which exertion of both 5-HT_{1A} agonistic action and 5-HT₃ antagonistic action is effective, such as, for example, IBS, FD, reflux esophagitis, anxiety, psychophysiologic disorder, emesis, pain, urinary

35 incontinence, anischuria and pollakiurea.

5- HT_{1A} agonistic activity and 5- HT_3 antagonistic activity of the compounds of the formula (I) provided by the present invention and the compounds of the formula (II) which are used in therapy of IBS following the present invention can be demonstrated by the following experiments.

(1) Affinity measurement of the compounds to human 5- HT_{1A} receptor (in vitro)

CHO cell membrane sample in which human 5- HT_{1A} receptor was expressed (purchased from Packard Bioscience) 0.25 mL (about 50 units) was added to 24.75 mL of incubation buffer solution A (an aqueous solution of a mixture of 50 mmols/L of Tris-hydrochloric acid, 10 mmols/L of magnesium sulfate, 0.5 mmols/L of EDTA and 0.1% ascorbic acid, whose pH was adjusted to 7.4 at 27°C with 1N-aqueous sodium hydroxide solution), and labeled as membrane sample suspension A. Separately, each test compound was made into 270 μmol /L DMSO solution and diluted to a prescribed concentration with the incubation buffer solution A, to provide a compound solution.

A piece of polypropylene tube was charged with 20 μL of [^3H]8-OH-DPAT (8-hydroxy-2-(di-n-propylamino)tetralin; purchased from Daiichi Pure Chemicals Co., Ltd.) (The concentration of the [^3H]8-OH-DPAT had been advancedly adjusted to render its concentration in the reaction mixture to 0.25 nmols/L) and 20 μL of one of the compound solutions. Further 500 μL of the membrane sample suspension A was added into the tube, followed by 60 minutes' incubation at 27°C. The reaction was terminated by rapid filtration of the reaction mixture through GF/C filter which had been advancedly immersed in a solution formed by adding to the incubation buffer solution A polyethyleneimine to a concentration of 0.3%, using Brandel cell harvester. Then the filter was washed with about 5 mL of 50 mmols/L of Tris-hydrochloric acid which had been cooled to 4°C. The filter was once again washed after similar operation.

Residual radioactivity on the filter was measured with

liquid scintillation counter (Aloka Co., LSC-5100). Percent inhibition (%) of each test compound to binding of [³H]8-OH-DPAT to 5-HT_{1A} receptor at a concentration of 0.25 nmols/L, i.e., affinity of each test compound to 5-HT_{1A} receptor, can be calculated according to the following expression. The ratio of non-specific binding was calculated by measuring the radioactivity in case of using 8-OH-DPAT at a concentration of 10 μmols/L, with which value the measured value of each test compound was compensated.

$$\left[1 - \frac{\text{radioactivity when each test compound was used}}{\text{radioactivity in the control experiment}} \times 100 \right]$$

(2) Measurement of affinity of each test compound to human 5-HT₃ receptor (in vitro):

HEK-293 cell membrane sample in which human 5-HT₃ receptor was expressed (purchased from BIOLINKS K.K.) 0.05 mL (about 50 microassay) was added to 24.95 mL of incubation buffer solution B (an aqueous solution of a mixture of 50 mmols/L of Tris-hydrochloric acid, 5 mmols/L of magnesium chloride and 1 mmol/L of EDTA, whose pH was adjusted to 7.5 at 25°C with 1N-aqueous sodium hydroxide solution) and homogenized, to provide a membrane sample suspension B. Separately, each test compound was made into 270 μmols/L of DMSO solution and diluted to a prescribed concentration with the incubation buffer solution B to provide a compound solution.

A piece of polypropylene tube was charged with 20 μL of [³H]BRL-43694 (purchased from Daiichi Pure Chemicals Co., Ltd.) (The concentration of [³H]BRL-43694 had been advancedly adjusted to render its concentration in the reaction mixture to 0.5 nmols/L.) and 20 μL of one of the compound solutions. Further 500 μL of the membrane sample suspension B was added into the tube, followed by 60 minutes' incubation at 25°C. The reaction was terminated by rapid filtration of the reaction mixture through GF/B filter which had been advancedly immersed in a solution formed by adding to the incubation buffer solution B polyethyleneimine to a concentration of

0.5%, using Brandel cell harvester. Then the filter was washed with about 5 mL of 50 mmols/L of Tris-hydrochloric acid which had been cooled to 4°C. The filter was once again washed after similar operation.

5 Residual radioactivity on the filter was measured with liquid scintillation counter (ALOKA CO., LTD. LSC-5100). Percent inhibition (%) of each test compound to binding of [³H]BRL-43694 to 5-HT₃ receptor at a concentration of 0.5 nmols/L, i.e., affinity of each test compound to 5-HT₃ receptor, can be calculated according to the
10 following expression. The ratio of non-specific binding was calculated by measuring the radioactivity in case of using tropisetron: (ICS 205-930) at a concentration of 10 μmols/L, with which value the measured value of each test compound was compensated.

$$15 \quad \left[1 - \frac{\text{radioactivity when each test compound was used}}{\text{radioactivity in the control experiment}} \times 100 \right]$$

Affinity of each test compound to 5-HT_{1A} receptor and 5-HT₃ receptor at a concentration of 100 nmols/L were as shown in the following Tables A-1 and A-2. BRL-43694 and tropisetron (ICS 205-930), which were used in measuring affinity of those compounds
20 to 5-HT₃ receptor, have the following structures:

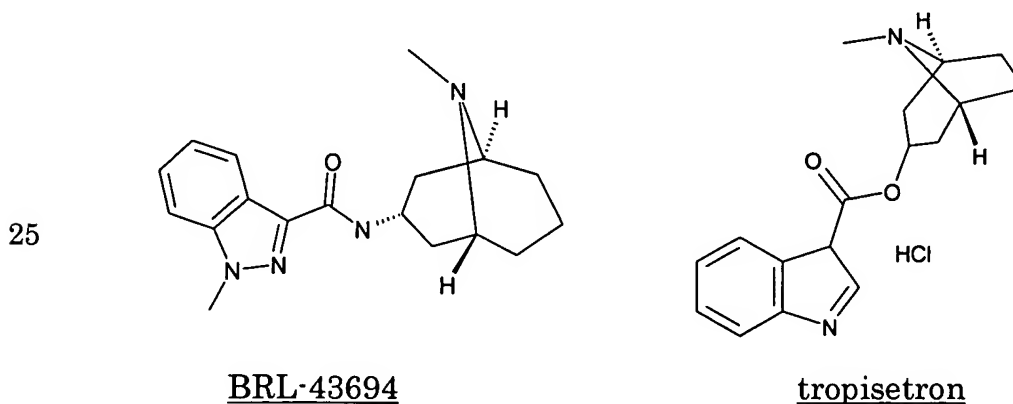


TABLE A-1

Compound	Percent Inhibition (%) on Each Receptor's Binding at 10^{-7}M	
	5-HT _{1A}	5-HT ₃
Example 1-1	94.5	94.0
Example 1-4	96.6	93.2
Example 1-5	85.0	82.6
Example 1-14	99.8	95.9
Example 1-24	95.7	79.6
Example 1-31	97.9	92.4
Example 1-33	94.0	94.2
Example 1-59	100.3	50.0
Example 2-1	60.8	52.6
Example 2-12	41.9	34.6
Example 2-14	57.7	51.9
Example 2-20	81.6	52.8
Example 3-1	77.0	96.9
Example 3-16	92.5	74.3
Example 4-1	100.7	81.2
Example 4-3	98.2	83.6
Example 4-4	98.7	78.6
Example 4-18	98.0	50.9
Example 4-20	94.3	87.8
Example 4-22	58.2	93.9
Example 4-23	97.0	79.3
Example 4-25	99.4	43.3
Example 4-28	97.6	45.1
Example 4-35	98.0	96.9
Example 4-36	90.4	87.7
Example 4-42	95.8	58.5
Example 4-56	96.9	50.2
Example 4-60	96.9	91.5
Example 4-61	96.8	88.7
Example 4-70	96.1	92.5
Example 5-1	74.0	94.8
Example 5-3	76.0	74.5
Example 5-8	54.5	85.5
Example 6-2	92.4	39.3
Example 7-1	97.5	94.2
Example 7-2	93.3	94.5
Example 7-3	85.8	84.7

Example 7-4	85.0	61.2
Example 7-5	53.0	6.3
Example 7-6	97.4	93.8
Example 7-7	96.9	95.0
Example 7-8	93.4	78.8
Example 7-9	91.0	32.0
Example 7-10	16.1	7.1
Example 7-11	45.0	24.7
Example 7-12	96.0	93.2
Example 7-13	90.2	93.6
Example 7-14	77.8	16.7
Example 7-15	62.1	35.0
Example 7-16	72.2	66.8
Example 7-17	50.6	1.9
Example 7-18	93.1	68.8
Example 7-19	85.0	7.4
Example 7-20	101.2	92.9
Example 7-21	97.4	95.0
Example 7-22	82.4	5.3
Example 7-23	77.0	74.8
Example 7-24	78.3	30.0
Example 7-25	97.5	99.7
Example 7-26	85.2	71.6
Example 7-27	87.0	90.2
Example 7-28	74.7	87.3
Example 7-29	80.8	93.6
Example 7-30	73.5	92.4

TABLE A-2

Compound	Percent Inhibition (%) on Each Receptor's Binding at 10^{-7} M	
	5-HT _{1A}	5-HT ₃
Production Example 1	86.7	80.8
Production Example 4	72.4	65.6
Production Example 6	90.1	97.5
Production Example 8	78.3	93.3
Production Example 10	98.5	73.8
Production Example 16	61.1	99.2
Production Example 17	83.6	82.9
Production Example 23	83.2	85.8
Production Example 25	83.2	65.5
Production Example 28	23.9	92.5
Production Example 30	92.8	93.4
Production Example 32	91.7	94.4
Production Example 37	57.3	70.2
Production Example 38	94.8	93.1
Production Example 40	42.9	99.3
Production Example 47	90.6	93.6
Production Example 49	88.7	96.3
Production Example 52	84.1	97.0
Production Example 57	88.9	96.5
Production Example 61	25.3	94.1
Production Example 63	80.4	96.8
Production Example 71	94.8	42.2
Production Example 72	96.7	99.8
Production Example 73	98.3	99.3
Production Example 74	94.6	98.9
Production Example 76	96.6	94.4
Production Example 77	98.9	97.9
Production Example 81	95.8	74.4
Production Example 82	99.3	90.3
Production Example 85	99.9	98.9
Production Example 87	96.4	96.9
Production Example 89	92.1	83.5
Production Example 98	88.2	60.8
Production Example 102	95.4	98.9
Production Example 103	91.4	99.5
Production Example 104	85.5	99.3
Production Example 105	72.7	96.4

Production Example 106	100.7	98.3
Production Example 107	98.5	95.9
Production Example 108	90.6	100.1
Production Example 109	75.4	92.5
Production Example 110	98.9	97.9
Production Example 111	48.0	95.5
Production Example 112	53.9	98.8
Production Example 113	56.4	82.4
Production Example 114	16.7	91.0
Production Example 115	82.0	74.3
Production Example 116	70.6	25.6
Production Example 117	57.7	10.6
Production Example 118	76.0	84.9
Production Example 119	33.7	71.9
Production Example 120	81.0	99.4
Production Example 121	69.3	85.6

(3) Measurement of 5-HT_{1A} receptor agonistic action on rats (in vivo):

- 5 Seven weeks old SD male rats were divided into 4 – 5 rats per group which were accustomed to the experimental environments twice. A week after the second accustomed, the rats were put into a transparent plastic case, and 10 mg/kg of a test compound (as dissolved in 1N-hydrochloric acid and diluted with
- 10 suitable amount of saline) was intraperitoneally administered thereto. Immediately before the administration and 5, 10, 20 and 30 minutes after the administration, behaviors of the rats were observed as to lower lip retraction (LLP) and flat body posture (FBP). The results were evaluated in 4 grades (0: no reaction, 1: feeble reaction, 2:
- 15 medium reaction, 3: maximum reaction). The maximum value of the evaluation points of each group was determined, with the result as shown in the following Tables B-1 and B-2.

TABLE B-1

Compound	5-HT _{1A} Receptor Agonistic Action on Rats	
	LLR	FBP
Example 4-1	1.5	1.8
Example 4-3	1.8	1.8
Example 4-4	2.8	2.6
Example 4-18	2.2	2.8
Example 4-25	0.8	1.0
Example 7-1	2.2	1.8
Example 7-2	0.2	0.4
Example 7-6	2.4	2.0
Example 7-7	2.2	2.2
Example 7-20	1.6	1.8

TABLE B-2

5

Compound	5-HT _{1A} Receptor Agonistic Action on Rats	
	LLR	FBP
Production Example 6	2.8	2.4
Production Example 8	2.0	0.8
Production Example 34	3.0	2.8
Production Example 49	2.2	1.8
Production Example 72	3.0	3.0
Production Example 73	2.4	2.2
Production Example 102	3.0	3.0
Production Example 103	3.0	0.4
Production Example 104	1.6	0.2
Production Example 107	2.8	3.0
Production Example 108	2.4	0.4

(4) Measurement of 5-HT₃ receptor antagonistic action on rats (in vivo)

10 SD male rats (weighing 270 – 410 g) were anesthetized by peritoneal administration of 1.25 g/kg of urethane (as dissolved in distilled water), and then catheters for measuring blood pressure and heart rate were inserted into their left carotid artery and a catheter for administration of test compound was inserted into their right
 15 carotid artery. After their blood pressure and heart rate were

stabilized, 300 µg/kg of 5-hydroxytryptamine creatinine sulfate (serotonin) was rapidly intravenously administered and thereby induced transient bradycardiac reaction (BC 1) was observed. When the blood pressure and heart rate were re-stabilized after the serotonic administration, the test compounds were intravenously administered to the rats. Ten minutes thereafter, 300 µg/kg of serotonin was once again rapidly intravenously administered and thereby induced transient bradycardiac reaction (BC 2) was observed. Percent inhibition of bradycardia manifestation of each test compound, i.e., BJ reflex inhibition, can be calculated according to the following expression:

$$\left[\frac{BC1 - BC2}{BC 1} \times 100 \right]$$

Bradycardia manifestation inhibition of each test compound was as shown in the following Tables C-1 and C-2.

TABLE C-1

Compound	Dose (mg/kg)	BC Inhibition (%)
Example 4-1	0.1	70.4
Example 4-3	1.0	90.1
Example 4-4	0.1	68.7
Example 4-18	0.1	35.6
Example 4-25	0.1	49.1
Example 7-1	0.1	90.3
Example 7-6	0.01	58.5
Example 7-7	1.0	85.4
Example 7-20	0.01	64.7

TABLE C-2

Compound	Dose (mg/kg)	BC Inhibition (%)
Production Example 34	1.0	92.0
Production Example 35	1.0	94.6
Production Example 38	1.0	82.9
Production Example 46	1.0	94.4
Production Example 47	1.0	89.9
Production Example 49	1.0	96.8
Production Example 50	1.0	86.8
Production Example 72	0.3	72.5
Production Example 73	0.01	52.2
Production Example 95	1.0	96.0
Production Example 102	3.0	61.5
Production Example 103	3.0	57.6
Production Example 104	10.0	46.1

5

(5) Measurement of defecation acceleration in rats under restraint stress

Six weeks old SD male rats were divided into 6 – 8 rats per groups, which were separately bred in five chained cages starting a day before the test, to accustomize them to the environments. Feed and drinking water were left for their free ingestion until the morning of the day on which the test was given. On the day of the experiment, test compounds were orally administered and positive control solution (the used compounds were dissolved in 1N-hydrochloric acid and diluted with a suitable amount of saline) was administered intraperitoneally. Five (5) minutes thereafter, under lightly anesthetized condition, the rats were placed under restraint stress, with their upper half of the bodies including the front feet immobilized with gum tape. The restraint stress loading was conducted for an hour, and the number of excrements discharged during that period was counted.

The average values in each group of the action of the compounds of the present invention on the stress defecation are

shown in the following Table D, in comparison with average values in each group of the actions of combinations of various 5-HT_{1A} agonistic agents and 5-HT₃ antagonistic agents, wherein the animal group administered with saline and not loaded with the restraint stress was labeled as normal group, and that administered with saline and loaded with the restraint stress, as control group.

Those compounds which were used as the positive control chemicals used in the acceleration of defecation in rats under restraint stress are identified with the following structures.

10

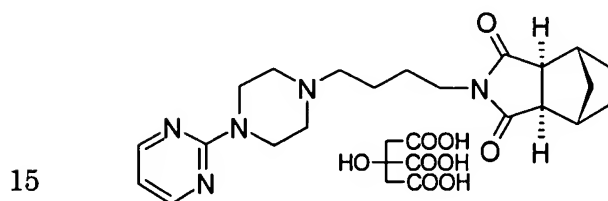
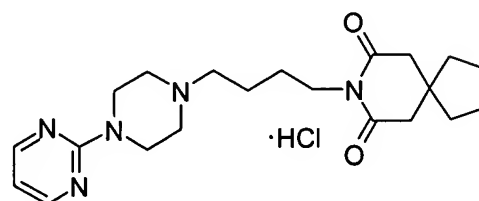
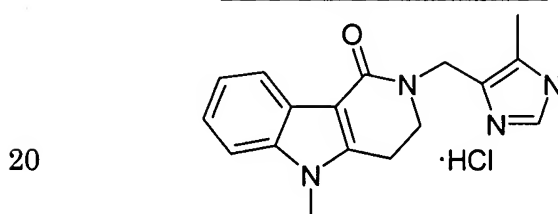
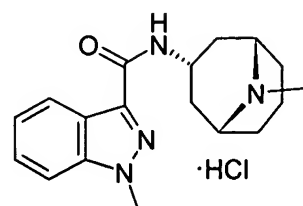
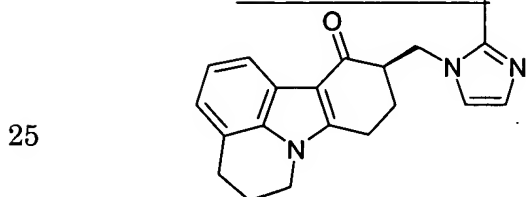
t a n d o s p i r o n eb u s p i r o n ea l o s e t r o ng r a n i s e t r o nc i l a n s e t r o n

TABLE D
Action of Compounds of Present Invention
on Defecation Under Stress

Compound	Dose	Number of excrements
Normal		1.7
Control		6.8
Example 4-1 (intraperitoneal administration)	0.3 mg/kg	5.3
	1 mg/kg	4.3
	3 mg/kg	2.1
Example 7-1 (oral administration)	1 mg/kg	5.8
	3 mg/kg	3.8
	10 mg/kg	2.3
Example 7-6 (oral administration)	1 mg/kg	5.4
	3 mg/kg	4.0
	10 mg/kg	2.9
Example 7-20 (oral administration)	1 mg/kg	5.4
	3 mg/kg	3.6
	10 mg/kg	2.4
tandospirone (intraperitoneal administration)	1 mg/kg	5.7
	3 mg/kg	4.3
	10 mg/kg	3.8
buspirone (intraperitoneal administration)	1 mg/kg	4.3
alosetron (intraperitoneal administration)	0.3 mg/kg	5.2
	1 mg/kg	4.1
	3 mg/kg	3.7
granisetron (intraperitoneal administration)	0.3 mg/kg	4.3
cilansetron (intraperitoneal administration)	1 mg/kg	4.0
tandospirone (3 mg/kg) + alosetron (1mg/kg) (intraperitoneal administration)		2.4
tandospirone (3 mg/kg) + granisetron (0.3 mg/kg) (intraperitoneal administration)		2.6
tandospirone (3 mg/kg) + cilansetron (1 mg/kg) (intraperitoneal administration)		2.3
buspirone (1 mg/kg) + alosetron (1 mg/kg) (intraperitoneal administration)		2.8
buspirone (1 mg/kg) + granisetron (0.3 mg/kg) (intraperitoneal administration)		2.3
buspirone (1 mg/kg) + cilansetron (1 mg/kg) (intraperitoneal administration)		2.9

Thus the pyrimidine derivatives represented by the formula (I) of the present invention or their pharmaceutically acceptable salts can be orally or parenterally (e.g., intramuscular injection, intravenous injection, intraperitoneal administration, rectal administration, subcutaneous injection or the like) administered to human beings and other mammals for therapy or treatment, as 5-HT₃ antagonistic agents having 5-HT_{1A} agonistic action. Also in the IBS-therapeutic method following the present invention, the 5-HT₃ antagonistic agent concurrently exhibiting 5-HT_{1A} agonistic activity can be orally or parenterally (e.g., intramuscular injection, intravenous injection, intraperitoneal administration, rectal administration, endermic administration or the like) administered, or 5-HT_{1A} agonistic agent and 5-HT₃ antagonistic agent can be similarly administered simultaneously, in sequence or at an interval, with the view to have cooperatively express 5-HT_{1A} agonistic activity and 5-HT₃ antagonistic activity on human beings or other mammals in vivo.

Where compounds of the present invention and the active compounds which are used in therapy of IBS following the present invention are used as medicine, they can be formulated into medical preparations with non-toxic adjuvants, of such forms suitable for intended utilities such as solid (e.g., tablet, hard capsule, soft capsule, granule, powder, grain, pill, troche and the like); semi-solid (e.g., suppository, ointment and the like); or liquid (e.g., injection, emulsion, suspension, lotion, spray and the like). As non-toxic adjuvants useful for the preparations, for example, starch, gelatin, glucose, lactose, fructose, maltose, magnesium carbonate, talc, magnesium stearate, methyl cellulose, carboxymethyl cellulose or salts thereof, gum Arabic, polyethylene glycol, p-hydroxybenzoic acid alkyl esters, syrup, ethanol, propylene glycol, Vaseline, Carbowax, glycerine, sodium chloride, sodium sulfite, sodium phosphate, citric acid and the like can be named. The medical preparations may also contain therapeutically useful other medicines.

Content of compounds of the present invention or active compounds used in the therapy of IBS following the present

invention in the medical preparations differs depending on the form of preparations. In general terms, for solid and semi-solid preparations it is desirable to use them at concentration levels of 0.1 – 50% by weight, and for liquid preparations, at the concentration levels of 0.05 – 10% by weight.

Dosage of compounds of the present invention or active compounds used in the therapy of IBS according to the present invention is variable over a broad range depending on the kind of object warm-blooded patients represented by human being, administration route, seriousness of symptoms, doctor's diagnosis and so on. In general terms, the dosage can be within a range of 0.01 – 5 mg/kg, preferably 0.02 – 2 mg/kg, per day. Whereas, of course dosages less than the above lower limit or more than the upper limit may be administered according to seriousness of individual patient, doctor's diagnosis and so on. Such a dosage can be administered once a day or in plural times as divided portions.

Examples

Hereinafter the present invention is more specifically explained, referring to working examples and formulation examples.

Example 1: Syntheses of compounds of the formula (I) in which X¹ stands for amino, lower alkylamino, di-lower alkylamino or lower alkylideneamino; and Y stands for sulfur

Example 1-1

Step 1-1-A:

To a solution formed by dissolving 4.31 g of anhydrous piperazine in 30 ml of ethylene glycol, 818 mg of 2-chloroquinoline was added, and stirred at 140°C for 2 hours. After cooling, saturated aqueous sodium hydrogencarbonate solution was added, and the system was extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate and the solvent was distilled off under reduced pressure. The residue was purified on silica gel column chromatography (chloroform: methanol = 2:1) to provide 1.09 g (100%) of 2-piperazin-1-ylquinoline.

¹H-NMR(CDCl₃)δ:7.89(d,J=9.2Hz,1H),7.70(d,J=8.4Hz,1H),
 7.59(dd,J=1.5Hz,8.0Hz,1H),
 7.53(ddd,J=1.5Hz,7.0Hz,8.4Hz,1H),7.26~7.22(m,1H),
 5 6.97(d,J=9.2Hz,1H),3.70(t,J=5.0Hz,4H),3.01(t,J=5.0Hz,4H)
 Mass,m/e:213(M⁺),145(base)

Step 1-1-B:

Dissolving 853 mg of 2-piperazin-1-ylquinoline as prepared in
 10 above Step 1-1-A in 5 ml of acetone, 5 ml of an aqueous solution
 containing 160 mg of sodium hydroxide was added to the solution,
 and into which 0.5 ml of 1-bromo-3-chloropropane was dropped,
 followed by stirring for an overnight at room temperature. Then
 diethyl ether was added, followed by washing with saturated aqueous
 15 sodium hydrogencarbonate solution, and the organic layer was dried
 over anhydrous magnesium sulfate. The solvent was distilled off
 under reduced pressure, and the residue was purified on silica gel
 column chromatography (chloroform : methanol = 50:1) to provide
 1.10 g (95%) of 2-[4-(3-chloropropyl)piperazin-1-yl]quinoline.

20

¹H-NMR(CDCl₃)δ:7.89(d,J=9.2Hz,1H),7.70(d,J=8.4Hz,1H),
 7.59(dd,J=1.4Hz,8.0Hz,1H),
 7.53(ddd,J=1.5Hz,7.1Hz,8.5Hz,1H),
 7.22(ddd,J=1.1Hz,6.9Hz,8.0Hz,1H),6.98(d,J=9.2Hz,1H),
 25 3.75(t,J=5.1Hz,4H),3.61(t,J=6.5Hz,2H),2.63~2.43(m,6H),
 2.04~1.97(m,2H)
 Mass,m/e:289(M⁺),157(base)

Step 1-1-C:

30 A mixture of 80 mg of potassium 3-amino-5,6-dimethyl-4-oxo-
 3,4-dihydrothieno[2,3-d]pyrimidine-2-thiolate, which was prepared
 from ethyl 2-amino-4,5-dimethylthiophene-3-carboxylate; 104 mg of
 2-[4-(3-chloropropyl)piperazin-1-yl]quinoline as prepared in the Step
 1-1-B; and 5 ml of ethanol, was heated under reflux for 4.5 hours.
 35 After cooling off the reaction mixture, chloroform was added, followed

by washing with saturated brine. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified on silica gel column chromatography (chloroform : methanol = 100:1) to provide 72 mg
 5 (50%) of 3-amino-5,6-dimethyl-2-[3-(4-quinolin-2-ylpiperazin-1-yl)-propylthio]-3H-thieno[2,3-d]pyrimidin-4-one.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.89(d, J=8.7Hz, 1H), 7.70(d, J=8.4Hz, 1H),
 7.59(d, J=8.1Hz, 1H), 7.54~7.52(m, 1H), 7.23~7.20(m, 1H),
 10 6.99(d, J=9.2Hz, 1H), 4.77(s, 2H), 3.79(t, J=5.1Hz, 4H),
 3.19(t, J=7.3Hz, 2H), 2.62(t, J=5.1Hz, 4H), 2.56(t, J=7.0Hz, 2H),
 2.45(s, 3H), 2.36(s, 3H), 2.00(q, J=7.3Hz, 2H)
 IR(KBr) ν_{max} : 3308, 2916, 1668, 1604, 1506 cm^{-1}
 Mass, m/e: 480(M^+), 157(base)

15

Example 1-2

In the manner similar to Example 1-1,
 3-amino-5,6-dimethyl-2-[3-(4-pyridin-2-ylpiperazin-1-yl)propylthio]-
 3H-thieno[2,3-d]pyrimidin-4-one was obtained.

20

melting point: 183.1 – 184.8°C
 $^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.19(ddd, J=0.6Hz, 1.9Hz, 4.9Hz, 1H),
 7.48(ddd, J=1.9Hz, 7.2Hz, 8.9Hz, 1H), 6.65(d, J=8.5Hz, 1H),
 6.62(ddd, J=0.8Hz, 4.9Hz, 7.1Hz, 1H), 4.77(s, 2H),
 25 3.57(t, J=5.0Hz, 4H), 3.18(t, J=7.1Hz, 2H), 2.59(t, J=5.1Hz, 4H),
 2.54(t, J=7.0Hz, 2H), 2.44(s, 3H), 2.36(s, 3H), 1.98(q, J=7.2Hz, 2H)
 IR(KBr) ν_{max} : 3500, 2920, 1660, 1592, 1504 cm^{-1}
 Mass, m/e: 430(M^+), 107(base)

30 Example 1-3

In the manner similar to Example 1-1,
 3-amino-2-[3-(4-pyridin-2-ylpiperazin-1-yl)propylthio]-5,6,7,8-
 tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyrimidine-4-one was obtained.

35 $^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.19(ddd, J=0.8Hz, 2.1Hz, 4.9Hz, 1H),

7.49~7.47(m,1H),6.65(d,J=8.8Hz,1H),6.63~6.61(m,1H),
 4.77(s,2H),3.57(t,J=5.2Hz,4H),3.17~3.15(m,2H),
 2.97~2.94(m,2H),2.77~2.73(m,2H),2.59(t,J=4.9Hz,4H),
 1.98(q,J=7.2Hz,2H),1.89~1.78(m,4H)
 5 IR(KBr) ν_{max} :3104,2940,1594,1506 cm^{-1}
 Mass,m/e:456(M^+),107(base)

Example 1-4

In the manner similar to Example 1-1,
 10 3-amino-2-[3-(4-quinolin-2-yl)piperazin-1-yl)propylthiol]-5,6,7,8-
 tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyrimidin-4-one was obtained.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$:7.88(d,J=8.7Hz,1H),7.70(d,J=7.8Hz,1H),
 7.59(dd,J=1.3Hz,8.0Hz,1H),7.53(m,1H),7.24~7.20(m,1H),
 15 6.99(d,J=9.2Hz,1H),4.77(s,2H),3.79(t,J=5.1Hz,4H),
 3.21~3.17(m,2H),2.99~2.95(m,2H),2.75~2.71(m,2H),
 2.62(t,J=5.1Hz,4H),2.56(t,J=7.0Hz,2H),1.99(q,J=7.3Hz,2H),
 1.91~1.80(m,4H)
 Mass,m/e:506(M^+),157(base)

20

Example 1-5

In the manner similar to Example 1-1,
 3-amino-5,6-dimethyl-2-[3-(4-pyrrolo[1,2-a]quinoxalin-4-yl)piperazin-
 1-yl)propylthiol]-3H-thieno[2,3-d]pyrimidin-4-one was obtained.

25

$^1\text{H-NMR}(\text{CDCl}_3)\delta$:7.82~7.81(m,1H),
 7.73(dd,J=1.5Hz,8.0Hz,1H),7.67(dd,J=1.5Hz,8.0Hz,1H),
 7.34~7.25(m,2H),6.80(dd,J=1.3Hz,3.9Hz,1H),6.77~6.75(m,1H),
 4.78(s,2H),3.85(t,J=4.9Hz,4H),3.20(t,J=7.2Hz,2H),
 30 2.68(t,J=4.9Hz,4H),2.68(t,J=7.2Hz,2H),2.44(s,3H),2.36(s,3H),
 2.04~1.96(m,2H)
 IR(KBr) ν_{max} :3468,1662,1510 cm^{-1}
 Mass,m/e:519(M^+),196(base)

35 Example 1-6

In the manner similar to Example 1-1,
3-amino-2-[3-(4-benzothiazol-2-ylpiperazin-1-yl)propylthio]-5,6-
dimethyl-3H-thieno[2,3-d]pyrimidin-4-one was obtained.

5 Melting point: 200.5 – 201.2°C
 ¹H-NMR(CDCl₃)δ:7.61~7.59(m,1H),7.57~7.55(m,1H),
 7.29(ddd,J=1.4Hz,7.5Hz,7.9Hz,1H),
 7.08(ddd,J=1.2Hz,7.5Hz,7.9Hz,1H),4.77(s,2H),
 3.68(t,J=5.1Hz,4H),3.18(t,J=7.4Hz,2H),2.62(t,J=5.1Hz,4H),
10 2.56~2.54(m,2H),2.44(d,J=0.7Hz,3H),2.36(d,J=0.9Hz,3H),
 2.00~1.94(m,2H)
 IR(KBr)ν_{max}:3200,2920,1666,1512cm⁻¹
 Mass,m/e:486(M⁺),128(base)

15 Example 1-7

 In the manner similar to Example 1-1,
3-amino-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylthio]-3H-thieno-
[3,2-d]pyrimidin-4-one was obtained.

20 ¹H-NMR(CDCl₃)δ:7.90(d,J=5.1Hz,1H),7.70(d,J=8.4Hz,1H),
 7.61~7.58(m,1H),7.53(ddd,J=1.5Hz,7.0Hz,8.4Hz,1H),
 7.23~7.21(m,1H),7.20(d,J=5.1Hz,1H),6.98(d,J=9.1Hz,1H),
 4.83(s,2H),3.79(t,J=4.9Hz,4H),3.22(t,J=7.3Hz,2H),
 2.63(t,J=4.9Hz,4H),2.59(t,J=7.3Hz,2H),2.03(q,J=7.3Hz,2H)
25 Mass,m/e:452(M⁺),157(base)

Example 1-8

 In the manner similar to Example 1-1,
3-amino-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylthio]-3H-
30 quinazolin-4-one was obtained.

¹H-NMR(CDCl₃)δ:8.22~8.19(m,1H),7.89(d,J=9.2Hz,1H),
 7.73~7.69(m,1H),7.61~7.51(m,3H),7.41~7.36(m,1H),
 7.24~7.20(m,1H),6.99(d,J=9.2Hz,1H),4.82(s,2H),
35 3.79(t,J=4.8Hz,4H),3.26(t,J=7.3Hz,2H),2.65~2.58(m,6H),

2.05(q, J=7.0Hz, 2H)

Mass, m/e: 446(M⁺), 157(base)

Example 1-9

5 In the manner similar to Example 1-1,
3-amino-5,6-dimethyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)but-2-
enylthio]-3H-thieno[2,3-d]pyrimidin-4-one was obtained.

¹H-NMR(CDCl₃) δ: 7.88(d, J=9.2Hz, 1H), 7.69(d, J=8.3Hz, 1H),
10 7.61~7.56(m, 1H), 7.55~7.50(m, 1H), 7.23~7.20(m, 1H),
6.95(d, J=9.2Hz, 1H), 5.92~5.85(m, 1H), 5.83~5.76(m, 1H),
4.76(s, 2H), 3.78(d, J=6.7Hz, 2H), 3.74(t, J=5.1Hz, 4H),
3.06(d, J=6.4Hz, 2H), 2.57(t, J=5.1Hz, 4H), 2.44(s, 3H), 2.35(s, 3H)
Mass, m/e: 492(M⁺), 157(base)

15

Example 1-10

In the manner similar to Example 1-1, ethyl
3-amino-4-oxo-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylthio]-3,4-
dihydroquinazoline-7-carboxylate was obtained.

20

¹H-NMR(CDCl₃) δ: 8.25(d, J=5.5Hz, 1H), 8.24(d, J=0.7Hz, 1H),
7.99(dd, J=1.5Hz, 8.4Hz, 1H), 7.88(d, J=9.2Hz, 1H),
7.70(d, J=8.1Hz, 1H), 7.61~7.58(m, 1H),
7.53(ddd, J=1.8Hz, 7.0Hz, 8.8Hz, 1H),
25 7.22(ddd, J=1.1Hz, 7.0Hz, 8.1Hz, 1H), 7.00(d, J=4.2Hz, 1H),
4.84(s, 2H), 4.44(q, J=7.3Hz, 2H), 3.80(t, J=5.1Hz, 4H),
3.28(t, J=7.0Hz, 2H), 2.65(t, J=5.1Hz, 4H), 2.60(t, J=7.0Hz, 2H),
2.08~2.01(m, 2H), 1.43(t, J=7.3Hz, 3H)
Mass, m/e: 518(M⁺), 157(base)

30

Example 1-11

In the manner similar to Example 1-1,
3-amino-5,6-dimethyl-2-[3-(4-phenanthridin-6-ylpiperazin-1-
yl)propylthio]-3H-thieno[2,3-d]pyrimidin-4-one was obtained.

35

¹H-NMR(CDCl₃)δ:8.55(d,J=8.4Hz,1H),
 8.42(dd,J=1.1Hz,8.1Hz,1H),8.21(d,J=7.3Hz,1H),
 7.92(dd,J=1.1Hz,8.1Hz,1H),7.79~7.75(m,1H),7.63~7.60(m,2H),
 7.50~7.46(m,1H),3.56(br s,4H),3.21(t,J=7.0Hz,2H),
 2.79(br s,4H),2.64(t,J=7.0Hz,2H),2.44(s,3H),2.35(s,3H)
 Mass,m/e:530(M⁺),207(base)

Example 1-12

In the manner similar to Example 1-1,
 3-amino-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylthio]-3,4,5,6,7,8-
 hexahydro-4,7-dioxa-9-thia-1,3-diaza-9H-fluorene was obtained.

¹H-NMR(CDCl₃)δ:7.89(d,J=9.1Hz,1H),7.70(d,J=8.1Hz,1H),
 7.69(d,J=7.9Hz,1H),7.53(ddd,J=1.3Hz,6.9Hz,8.2Hz,1H),
 7.24~7.20(m,1H),4.78(s,4H),4.02~4.00(m,2H),
 3.79(t,J=5.0Hz,4H),3.22~3.07(m,2H),2.62(t,J=5.0Hz,4H),
 2.57(t,J=6.8Hz,2H),2.04~1.96(m,2H)
 Mass,m/e:508(M⁺),157(base)

Example 1-13

In the manner similar to Example 1-1,
 3-amino-7-tert-butoxycarbonyl-2-[3-(4-quinolin-2-ylpiperazin-1-
 yl)propylthio]-3,4,5,6,7,8-hexahydro-4-oxa-9-thia-1,3,7-triaza-
 9H-fluorene was obtained.

¹H-NMR(CDCl₃)δ:7.89(d,J=9.2Hz,1H),7.70(d,J=8.4Hz,1H),
 7.61~7.58(m,1H),7.53(ddd,J=1.5Hz,7.0Hz,8.4Hz,1H),
 7.24~7.20(m,1H),6.99(d,J=9.2Hz,1H),4.78(s,2H),4.60(br s,2H),
 3.79(t,J=5.1Hz,4H),3.73~3.70(m,2H),3.22~3.18(m,2H),
 3.06(br s,2H),2.62(t,J=5.1Hz,4H),2.58~2.54(m,2H),
 2.00(q,J=7.3Hz,2H)
 Mass,m/e:607(M⁺),157(base)

Example 1-14

In the manner similar to Example 1-1,

3-amino-5-methyl-4-oxo-2-[3-(4-quinolin-2-ylpiperazin-1-yl)-propylthio]-3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxylic acid ethyl ester was obtained.

- 5 $^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.89(d, J=8.8Hz, 1H), 7.70(d, J=8.4Hz, 1H),
 7.61~7.55(m, 1H), 7.53(ddd, J=1.5Hz, 7.0Hz, 8.4Hz, 1H),
 7.22(ddd, J=1.1Hz, 7.0Hz, 8.1Hz, 1H), 6.99(d, J=9.2Hz, 1H),
 4.78(s, 2H), 4.36(q, J=7.3Hz, 2H), 3.79(t, J=5.1Hz, 4H),
 3.23~3.19(m, 2H), 2.91(s, 3H), 2.66~2.63(m, 4H), 2.61~2.57(m, 2H),
 10 2.05~1.98(m, 2H), 1.40(t, J=7.3Hz, 3H)
 Mass, m/e: 538(M^+), 157(base)

Example 1-15

In the manner similar to Example 1-1,

- 15 3-amino-2-[3-(4-benzothiazol-2-ylpiperazin-1-yl)propylthio]-5,6,7,8-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyrimidin-4-one was obtained.

- $^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.59(dd, J=1.2Hz, 7.7Hz, 1H),
 7.54(dd, J=1.2Hz, 8.1Hz, 1H), 7.29~7.27(m, 1H), 7.07~7.05(m, 1H),
 20 4.76(s, 2H), 3.68~3.66(m, 4H), 3.19~3.15(m, 2H), 2.97~2.94(m, 2H),
 2.73(t, J=5.8Hz, 2H), 2.60(t, J=5.1Hz, 4H), 2.55(t, J=6.9Hz, 2H),
 1.96(q, J=7.0Hz, 2H), 1.90~1.83(m, 4H)
 Mass, m/e: 512(M^+), 163(base)

Example 1-16

In the manner similar to Example 1-1,

3-amino-7-nitro-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylthio]-3H-quinazolin-4-one was obtained.

- 30 $^1\text{H-NMR}(\text{DMSO}-d_6)\delta$: 8.29(d, J=8.9Hz, 1H), 8.23(d, J=2.2Hz, 1H),
 8.12(dd, J=2.2Hz, 8.9Hz, 1H), 8.02(d, J=9.2Hz, 1H),
 7.67(d, J=7.2Hz, 1H), 7.56~7.40(m, 2H), 7.23~7.18(m, 2H),
 5.84(s, 2H), 3.72(t, J=4.8Hz, 4H), 3.17(t, J=7.3Hz, 2H),
 2.55~2.48(m, 6H), 1.93(t, J=7.3Hz, 2H)
 35 Mass, m/e: 491(M^+), 157(base)

Example 1-17

In the manner similar to Example 1-1,
 3-amino-2-[3-(4-benzothiazol-2-ylpiperazin-1-yl)propylthio]-7-nitro-
 5 3H-quinazolin-4-one was obtained.

$^1\text{H-NMR}(\text{DMSO}-d_6)\delta$: 8.30(d, J=8.5Hz, 1H), 8.23(d, J=2.2Hz, 1H),
 8.14(dd, J=2.2Hz, 8.8Hz, 1H), 7.75(d, J=6.9Hz, 1H),
 7.45(d, J=7.5Hz, 1H), 7.29~7.25(m, 1H), 7.08~7.04(m, 1H),
 10 5.85(s, 2H), 3.62~3.59(m, 4H), 3.19~3.15(m, 2H), 2.51~2.49(m, 6H),
 1.93(t, J=7.3Hz, 2H)
 Mass, m/e: 497(M^+), 163(base)

Example 1-18

15 In the manner similar to Example 1-1,
 3-amino-2-[3-(4-benzothiazol-2-ylpiperazin-1-yl)propylthio]-
 3,4,5,6,7,8-hexahydro-4,7-dioxa-9-thia-1,3-diaza-9H-fluorene was
 obtained.

20 $^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.65~7.51(m, 2H), 7.38~7.13(m, 2H),
 4.78(s, 2H), 4.00(t, J=5.5Hz, 2H), 3.74~3.54(m, 4H),
 3.27~3.02(m, 4H), 2.67~2.49(m, 6H), 2.13~1.88(m, 2H),
 1.62(m, 2H),
 Mass, m/e: 514(M^+), 163(base)

25

Example 1-19

In the manner similar to Example 1-1,
 3-amino-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylthio]-3H-pyrido-
 [2,3-d]pyrimidin-4-one was obtained.

30

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.77(dd, J=1.5Hz, 4.4Hz, 1H),
 7.92(dd, J=1.5Hz, 8.4Hz, 1H), 7.89(d, J=9.2Hz, 1H),
 7.70(d, J=8.4Hz, 1H), 7.64~7.59(m, 2H),
 7.54(ddd, J=1.5Hz, 7.0Hz, 8.4Hz, 1H), 7.25~7.21(m, 1H),
 35 6.99(d, J=9.2Hz, 1H), 4.94(s, 2H), 3.79(t, J=5.1Hz, 4H),

3.27(t, J=7.3Hz, 2H), 2.64(t, J=5.1Hz, 4H), 2.60(t, J=7.3Hz, 2H),
 2.05(q, J=7.3Hz, 2H)
 Mass, m/e: 447(M⁺), 157(base)

5 Example 1-20

In the manner similar to Example 1-1,
 3-amino-7-tert-butoxycarbonyl-2-[3-(4-benzothiazol-2-ylpiperazin-1-yl)propylthio]-3,4,5,6,7,8-hexahydro-4-oxa-9-thia-1,3,7-triaza-9H-fluorene was obtained.

10

¹H-NMR(CDCl₃) δ: 7.60(dd, J=0.7Hz, 7.7Hz, 1H),
 7.56(d, J=8.1Hz, 1H), 7.31~7.29(m, 1H), 7.10~7.06(m, 1H),
 4.78~4.76(m, 2H), 4.61~4.59(m, 2H), 3.73~3.68(m, 6H),
 3.21~3.18(m, 2H), 3.06(br s, 2H), 2.63~2.61(m, 4H),
 2.57(t, J=7.0Hz, 2H), 2.05~1.96(m, 2H), 1.50(s, 9H)
 Mass, m/e: 613(M⁺), 56(base)

15

Example 1-21

In the manner similar to Example 1-1,
 3-amino-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylthio]-3H-pyrido[3,2-d]pyrimidin-4-one was obtained.

20

¹H-NMR(CDCl₃) δ: 8.92(dd, J=1.8Hz, 4.4Hz, 1H),
 8.55(dd, J=1.8Hz, 8.1Hz, 1H), 7.88(d, J=8.8Hz, 1H),
 7.70(d, J=8.4Hz, 1H), 7.59(dd, J=1.1Hz, 8.1Hz, 1H),
 7.53(ddd, J=1.5Hz, 7.0Hz, 8.4Hz, 1H), 7.37~7.34(m, 1H),
 7.24~7.20(m, 1H), 6.98(d, J=9.1Hz, 1H), 4.84(s, 2H),
 3.78(t, J=5.1Hz, 4H), 3.38(t, J=7.3Hz, 2H), 2.64~2.59(m, 6H),
 2.07(q, J=7.3Hz, 2H)
 Mass, m/e: 447(M⁺), 157(base)

25

30

Example 1-22

In the manner similar to Example 1-1,
 3-amino-2-[3-(4-benzothiazol-2-ylpiperazin-1-yl)propylthio]-3H-pyrido[2,3-d]pyrimidin-4-one was obtained.

35

¹H-NMR(DMSO-d₆)δ:8.69(dd,J=1.5Hz,4.4Hz,1H),
 7.95~7.92(m,1H),7.76~7.71(m,2H),7.44~7.42(m,2H),
 7.28~7.24(m,2H),7.07~7.03(m,2H),5.81(s,2H),
 3.57(t,J=5.1Hz,4H),3.15~3.11(m,2H),2.55~2.52(m,4H),
 2.50~2.44(m,2H),1.92~1.89(m,2H)
 Mass,m/e:453(M⁺),163(base)

Example 1-23

In the manner similar to Example 1-1,
 3-amino-2-[3-(4-benzothiazol-2-ylpiperazin-1-yl)propylthio-3H-
 pyrido[3,2-d]pyrimidin-4-one was obtained.

¹H-NMR(DMSO-d₆)δ:8.87(dd,J=1.8Hz,5.3Hz,1H),
 8.45(dd,J=1.8Hz,8.1Hz,1H),7.73(d,J=8.1Hz,1H),
 7.45~7.42(m,2H),7.28~7.24(m,1H),7.07~7.03(m,1H),
 5.76(s,2H),3.59~3.57(m,4H),3.17~3.14(m,2H),
 2.56(br s,4H),2.53~2.48(m,2H),1.94~1.90(m,2H)
 Mass,m/e:453(M⁺),163(base)

Example 1-24

In the manner similar to Example 1-1,
 3-amino-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylthio]-
 3,4,5,6,7,8,9,10-octahydro-4-oxa-11-thia-1,3-diaza-11H-cycloocta[a]-
 indene was obtained.

¹H-NMR(CDCl₃)δ:7.99(d,J=9.0Hz,1H),7.70(d,J=9.0Hz,1H),
 7.59(d,J=8.0Hz,1H),7.54~7.53(m,1H),7.24~7.22(m,1H),
 6.99(d,J=9.2Hz,1H),4.78(s,2H),3.79(t,J=5.1Hz,4H),
 3.21~3.18(m,2H),3.09(t,J=6.4Hz,2H),2.64~2.62(m,2H),
 2.63(t,J=5.1Hz,4H),2.59~2.55(m,2H),2.04~1.99(m,2H),
 1.72~1.69(m,4H),1.57~1.47(m,2H),1.34~1.26(m,2H)
 Mass,m/e:534(M⁺),157(base)

Example 1-25

In the manner similar to Example 1-1,
3-amino-2-[3-(4-benzothiazol-2-ylpiperazin-1-yl)propylthio]-
3,4,5,6,7,8,9,10-octahydro-4-oxa-11-thia-1,3-diaza-11H-cycloocta[a]-
indene was obtained.

5

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.58(d, J=0.7Hz, 1H), 7.56(d, J=2.1Hz, 1H),
7.32~7.28(m, 1H), 7.10~7.08(m, 1H), 4.79(s, 2H), 3.73(br s, 4H),
3.20~3.17(m, 2H), 3.08~3.04(m, 2H), 2.85~2.82(m, 2H),
2.68(br s, 4H), 2.62(br s, 2H), 2.04~2.02(m, 2H),
1.72~1.69(m, 4H), 1.47~1.43(m, 2H), 1.36~1.37(m, 2H)
Mass, m/e: 540(M^+), 163(base)

10

Example 1-26

In the manner similar to Example 1-1,
3-amino-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylthio]-3,4,5,6,7-
pentahydro-4-oxa-8-thia-1,3-diaza-8H-cyclopenta[a]indene was
obtained.

15

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.89(d, J=9.2Hz, 1H), 7.70(d, J=8.1Hz, 1H),
7.59(d, J=8.1Hz, 1H), 7.53(ddd, J=1.5Hz, 7.0Hz, 8.4Hz, 1H),
7.24~7.20(m, 1H), 6.99(d, J=9.2Hz, 1H), 4.80(s, 2H),
3.78(t, J=5.1Hz, 4H), 3.22~3.18(m, 2H), 3.04(t, J=7.3Hz, 2H),
2.94(t, J=7.3Hz, 2H), 2.62(t, J=5.1Hz, 4H), 2.59~2.55(m, 2H),
2.46(q, J=7.0Hz, 2H), 2.00(q, J=7.3Hz, 2H)
Mass, m/e: 492(M^+), 157(base)

20

25

Example 1-27

In the manner similar to Example 1-1,
3-amino-2-[3-[4-(4-methylquinolin-2-yl)piperazin-1-yl]propylthio]-
3,4,5,6,7-pentahydro-4-oxa-8-thia-1,3-diaza-8H-cyclopenta[a]indene
was obtained.

30

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.77(dd, J=1.3Hz, 8.2Hz, 1H),
7.72~7.70(m, 1H), 7.53(ddd, J=1.3Hz, 3.0Hz, 8.2Hz, 1H),
7.25~7.22(m, 1H), 6.85(s, 1H), 4.80(s, 2H), 3.78(t, J=5.1Hz, 4H),

35

3.22~3.18(m,2H),3.04(t,J=7.3Hz,2H),2.94(t,J=7.3Hz,2H),
 2.61(t,J=5.1Hz,4H),2.60(s,3H),2.56(t,J=7.3Hz,2H),
 2.50~2.42(m,2H),2.00(q,J=7.3Hz,2H)
 Mass,m/e:506(M⁺),171(base)

5

Example 1-28

In the manner similar to Example 1-1,
 3-amino-2-[3-(4-benzothiazol-2-ylpiperazin-1-yl)propylthio]-3,4,5,6,7-
 pentahydro-4-oxa-8-thia-1,3-diaza-8H-cyclopenta[a]indene was
 10 obtained.

¹H-NMR(CDCl₃)δ:7.60(dd,J=0.7Hz,7.7Hz,1H),
 7.56(d,J=1.3Hz,1H),7.32~7.28(m,1H),7.10~7.06(m,1H),
 4.80(s,2H),3.69(t,J=5.1Hz,4H),3.21~3.17(m,2H),
 15 3.06~3.02(m,2H),2.94(t,J=7.3Hz,2H),2.62(t,J=5.1Hz,4H),
 2.56(t,J=6.1Hz,4H),2.46(q,J=7.3Hz,2H),1.98(q,J=7.0Hz,2H)
 Mass,m/e:498(M⁺),128(base)

Example 1-29

20 In the manner similar to Example 1-1,
 3-amino-5-methyl-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylthio]-
 5,6,7,8-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyrimidin-4-one was
 obtained.

25 ¹H-NMR(CDCl₃)δ:7.89(d,J=9.2Hz,1H),7.70(d,J=8.4Hz,1H),
 7.59(d,J=8.1Hz,1H),7.55~7.51(m,1H),7.24~7.22(m,1H),
 6.99(d,J=9.2Hz,1H),4.79(s,2H),3.79(t,J=5.1Hz,4H),
 3.22~3.17(m,2H),2.80~2.69(m,1H),2.62(t,J=5.1Hz,4H),
 2.56(t,J=7.0Hz,2H),2.01~1.57(m,6H),1.30(d,J=6.0Hz,3H)
 30 Mass,m/e:520(M⁺),157(base)

Example 1-30

In the manner similar to Example 1-1,
 3-amino-6-methyl-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylthio]-
 35 5,6,7,8-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyrimidin-4-one was

obtained.

¹H-NMR(CDCl₃)δ:7.89(d,J=9.2Hz,1H),7.70(d,J=8.4Hz,1H),
7.60~7.58(m,1H),7.53(ddd,J=1.5Hz,7.0Hz,8.4Hz,1H),
5 7.22(ddd,J=1.1Hz,7.0Hz,8.1Hz,1H),6.99(d,J=9.2Hz,1H),
4.77(s,2H),3.79(t,J=5.1Hz,4H),3.19(t,J=7.3Hz,2H),
2.63~2.62(m,1H),2.62~2.60(m,4H),2.56(t,J=7.0Hz,2H),
2.04~1.92(m,6H),1.00(d,J=6.6Hz,3H)
Mass,m/e:520(M⁺),157(base)

10

Example 1-31

In the manner similar to Example 1-1,
3-amino-7-methyl-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylthio]-
5,6,7,8-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyrimidin-4-one was
15 obtained.

¹H-NMR(CDCl₃)δ:7.89(d,J=9.2Hz,1H),7.69(m,1H),
7.59(d,J=7.9Hz,1H),7.53(d,J=7.9Hz,1H),7.53(m,1H),
7.22(m,1H),6.99(d,J=9.2Hz,1H),4.77(s,2H),3.78(t,J=5.1Hz,4H),
20 3.21~3.18(m,3H),2.90~2.80(m,2H),2.62(t,J=5.1Hz,4H),
2.56(t,J=7.0Hz,2H),2.41~2.35(m,2H),2.04~1.98(m,4H),
1.10(d,J=6.6Hz,3H)
Mass,m/e:520(M⁺),157(base)

25 Example 1-32

In the manner similar to Example 1-1,
3-amino-5,6-dimethyl-2-[3-[4-(4-methylquinolin-2-yl)piperazin-1-
yl]propylthio]-3H-thieno[2,3-d]pyrimidin-4-one was obtained.

¹H-NMR(CDCl₃)δ:7.77(dd,J=1.1Hz,8.1Hz,1H),
7.71(d,J=7.7Hz,1H),7.53(ddd,J=1.5Hz,7.0Hz,8.4Hz,1H),
7.25~7.22(m,1H),6.84(d,J=3.7Hz,1H),4.78(s,2H),
3.78(t,J=5.1Hz,4H),3.20~3.17(m,2H),2.62~2.60(m,4H),
2.60(s,3H),2.58~2.54(m,2H),2.44(d,J=0.7Hz,3H),
30 2.36(d,J=0.7Hz,3H),1.99(q,J=7.3Hz,2H)

35

Mass, m/e: 494(M⁺), 171(base)

Example 1-33

In the manner similar to Example 1-1,

- 5 3-amino-2-[3-[4-(4-methylquinolin-2-yl)piperazin-1-yl]propylthio]-5,6,7,8-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyrimidin-4-one was obtained.

¹H-NMR(CDCl₃)δ: 7.77(dd, J=1.1Hz, 8.4Hz, 1H),
 10 7.71(d, J=8.4Hz, 1H), 7.52(ddd, J=1.5Hz, 7.0Hz, 8.4Hz, 1H),
 7.25~7.22(m, 1H), 6.85(s, 1H), 4.77(s, 2H), 3.78(t, J=5.1Hz, 4H),
 3.19(t, J=7.3Hz, 2H), 2.98~2.95(m, 2H), 2.75(t, J=5.9, 2H),
 2.62~2.60(m, 4H), 2.60(s, 3H), 2.56(t, J=7.3Hz, 2H),
 2.44(d, J=0.7Hz, 3H), 2.36(d, J=0.7Hz, 3H), 1.99(q, J=7.3Hz, 2H),
 15 1.89~1.83(m, 4H)
 Mass, m/e: 520(M⁺), 171(base)

Example 1-34

In the manner similar to Example 1-1,

- 20 3-amino-2-[3-[4-(4-methylquinolin-2-yl)piperazin-1-yl]propylthio]-3,4,5,6,7,8-hexahydro-4,7-dioxa-9-thia-1,3-diaza-9H-fluorene was obtained.

¹H-NMR(CDCl₃)δ: 7.77(dd, J=1.1Hz, 8.0Hz, 1H),
 25 7.70(d, J=8.4Hz, 1H), 7.53(ddd, J=1.5Hz, 7.0Hz, 8.4Hz, 1H),
 7.25~7.23(m, 1H), 6.84(s, 1H), 4.78(br s, 4H), 4.13~3.99(m, 2H),
 3.78(t, J=5.1Hz, 4H), 3.22~3.18(m, 2H), 3.10~3.07(m, 2H),
 2.63~2.55(m, 6H), 2.60(s, 3H), 2.04~1.97(m, 2H)
 Mass, m/e: 522(M⁺), 171(base)

30

Example 1-35

In the manner similar to Example 1-1,

- 3-amino-5,6-dimethyl-2-[3-[4-(5,6,7,8-tetrahydroquinolin-2-yl)piperazin-1-yl]propylthio]-3H-thieno[2,3-d]pyrimidin-4-one was
 35 obtained.

¹H-NMR(CDCl₃)δ:7.17(d,J=8.4Hz,1H),6.43(d,J=8.4Hz,1H),
 4.77(s,2H),3.50(t,J=5.1Hz,4H),3.17(t,J=7.3Hz,2H),
 2.75(t,J=5.6Hz,2H),2.63~2.52(m,8H),2.44(s,3H),
 2.35(d,J=7.0Hz,3H),1.97(q,J=7.3Hz,1H),1.86~1.80(m,2H),
 1.78~1.75(m,2H)
 Mass,m/e:484(M⁺),161(base)

Example 1-36

In the manner similar to Example 1-1,
 3-amino-2-[3-[4-(5,6,7,8-
 tetrahydroquinolin-2-yl)piperazin-1-yl]propylthio]-5,6,7,8-
 tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyrimidin-4-one was obtained.

¹H-NMR(CDCl₃)δ:7.17(d,J=8.4Hz,1H),6.44(d,J=8.4Hz,1H),
 4.77(s,2H),3.51(t,J=5.1Hz,4H),3.17(t,J=7.3Hz,2H),
 2.98~2.95(m,2H),2.75~2.73(m,2H),2.62~2.52(m,8H),
 1.98(q,J=7.3Hz,1H),1.89~1.72(m,8H)
 Mass,m/e:510(M⁺),161(base)

Example 1-37

In the manner similar to Example 1-1,
 3-amino-2-[3-[4-(5,6,7,8-tetrahydroquinolin-2-yl)piperazin-1-yl]-
 propylthio]-3,4,5,6,7-pentahydro-4-oxa-8-thia-1,3-diaza-8H-
 cyclopenta[a]indene was obtained.

¹H-NMR(CDCl₃)δ:7.18(d,J=8.4Hz,1H),6.44(d,J=8.4Hz,1H),
 4.81(s,2H),3.52(t,J=5.1Hz,4H),3.18(t,J=7.3Hz,2H),
 2.95~2.91(m,2H),2.76~2.57(m,6H),2.46(q,J=7.3Hz,2H),
 2.01(q,J=7.3Hz,2H),1.86~1.68(m,8H)
 Mass,m/e:496(M⁺),161(base)

Example 1-38

In the manner similar to Example 1-1,
 3-amino-2-[3-[4-(7-methoxyisoquinolin-1-yl)piperazin-1-

yl]propylthiol]-5,6-dimethyl-3H-thieno[2,3-d]pyrimidin-4-one was obtained.

¹H-NMR(CDCl₃)δ:8.07(d,J=5.8Hz,1H),7.68(d,J=8.0Hz,1H),
 5 7.40(d,J=2.3Hz,1H),7.30~7.27(m,1H),7.21(d,J=5.8Hz,1H),
 4.78(s,2H),3.94(s,3H),3.44(br s,4H),3.20(t,J=7.3Hz,2H),
 2.78(br s,4H),2.64(t,J=7.3Hz,2H),2.44(s,3H),2.35(s,3H),
 2.02(q,J=7.3Hz,2H)
 Mass,m/e:510(M⁺),187(base)

10

Example 1-39

In the manner similar to Example 1-1,
 3-amino-2-[3-[4-(7-methoxyisoquinolin-1-yl)piperazin-1-yl]
 yl]propylthiol]-5,6,7,8-tetrahydro-3H-benzo[4,5]thieno[2,3-d]-
 15 pyrimidin-4-one was obtained.

¹H-NMR(CDCl₃)δ:8.07(d,J=5.8Hz,1H),7.68(d,J=8.9Hz,1H),
 7.40(d,J=2.3Hz,1H),7.30~7.27(m,1H),7.21(d,J=5.4Hz,1H),
 4.78(s,2H),3.94(s,3H),3.45(br s,4H),3.20(t,J=7.0Hz,2H),
 20 2.98~2.96(m,2H),2.79(br s,4H),2.73~2.71(m,2H),
 2.65(t,J=7.0Hz,2H),2.03(q,J=7.3Hz,2H),1.86~1.82(m,4H)
 Mass,m/e:536(M⁺),187(base)

Example 1-40

25 In the manner similar to Example 1-1,
 3-amino-2-[3-[4-(7-methoxyisoquinolin-1-yl)piperazin-1-yl]-
 propylthiol]-3H-pyrido[2,3-d]pyrimidin-4-one was obtained.

¹H-NMR(CDCl₃)δ:8.70(dd,J=1.5Hz,4.6Hz,1H),
 30 7.92~7.91(m,1H),7.69~7.66(m,1H),7.63~7.57(m,1H),
 7.40~7.34(m,1H),7.30~7.20(m,2H),4.93(s,2H),3.91(s,3H),
 3.48~3.44(m,4H),3.30~3.26(m,2H)
 Mass,m/e:477(M⁺),187(base)

35 Example 1-41

In the manner similar to Example 1-1,
3-amino-2-[3-[4-(7-methoxyisoquinolin-1-yl)piperazin-1-yl]-
propylthio]-3H-pyrido[3,2-d]pyrimidin-4-one was obtained.

5 $^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.99~8.90(m, 1H), 8.56~8.54(m, 1H),
8.06(d, J=5.4Hz, 1H), 7.69~7.67(m, 2H), 7.40~7.21(m, 3H),
4.84(s, 2H), 3.94(s, 3H), 3.45~3.38(m, 6H), 2.79(br s, 4H),
2.78~2.70(m, 2H), 2.10~2.05(m, 2H)
Mass, m/e: 477(M^+), 187(base)

10

Example 1-42

In the manner similar to Example 1-1,
3-amino-2-[3-[4-(7-methoxy-3-methylisoquinolin-1-yl)piperazin-
1-yl]propylthio]-5,6-dimethyl-3H-thieno[2,3-d]pyrimidin-4-one was
15 obtained.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.58(d, J=8.9Hz, 1H), 7.34(br s, 1H),
7.23(dd, J=2.7Hz, 8.9Hz, 1H), 7.04(s, 1H), 4.77(s, 2H), 3.92(s, 3H),
3.46(br s, 4H), 3.21(t, J=7.3Hz, 2H), 2.78(br s, 4H),
20 2.65~2.63(m, 2H), 2.53(s, 3H), 2.44(s, 3H), 2.35(s, 3H),
2.04(br s, 2H)
Mass, m/e: 524(M^+), 188(base)

Example 1-43

25 In the manner similar to Example 1-1,
3-amino-2-[3-[4-(7-methoxy-3-methylisoquinolin-1-yl)piperazin-1-
yl]propylthio]-5,6,7,8-tetrahydro-3H-benzo[4,5]thieno[2,3-d]-
pyrimidin-4-one was obtained.

30 $^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.57(d, J=8.7Hz, 1H), 7.34(d, J=1.5Hz, 1H),
7.22(dd, J=2.3Hz, 8.9Hz, 1H), 7.04(s, 1H), 4.77(s, 2H), 3.92(s, 3H),
3.46(br s, 4H), 3.20(t, J=7.3Hz, 2H), 2.96(m, 2H),
2.77(br s, 4H), 2.74~2.71(m, 2H), 2.62~2.53(m, 2H), 2.53(s, 3H),
2.10(br s, 2H), 1.86~1.85(m, 2H)
35 Mass, m/e: 550(M^+), 188(base)

Example 1-44

In the manner similar to Example 1-1,
 3-amino-2-[3-[4-(5-methoxyisoquinolin-1-yl)piperazin-1-yl]-
 5 propylthio]-5,6-dimethyl-3H-thieno[2,3-d]pyrimidin-4-one was
 obtained.

¹H-NMR(CDCl₃)δ:8.17(d,J=5.8Hz,1H),7.68~7.63(m,2H),
 7.42(d,J=8.1Hz,1H),6.95(d,J=7.7Hz,1H),4.79(s,2H),4.00(s,3H),
 10 3.47(br s,4H),3.21(t,J=6.9Hz,2H),2.77(br s,4H),
 2.64(t,J=7.3Hz,2H),2.46(s,3H),2.36(s,3H),2.03(q,J=7.3Hz,1H)
 Mass,m/e:510(M⁺),187(base)

Example 1-45

15 In the manner similar to Example 1-1,
 3-amino-2-[3-[4-(5-methoxyisoquinolin-1-yl)piperazin-1-yl]-
 propylthio]-5,6,7,8-tetrahydro-3H-benzo[4,5]thieno[2,3-d]-
 pyrimidin-4-one was obtained.

20 ¹H-NMR(CDCl₃)δ:8.17(d,J=5.8Hz,1H),7.68~7.63(m,2H),
 7.44~7.40(m,1H),6.95(d,J=7.7Hz,1H),4.78(s,2H),4.00(s,3H),
 3.47(br s,4H),3.21(t,J=7.3Hz,2H),2.99~2.96(m,2H),
 2.76~2.74(m,6H),2.64(t,J=7.3Hz,2H),2.06~2.00(m,2H)
 Mass,m/e:536(M⁺),187(base)

25

Example 1-46

In the manner similar to Example 1-1,
 3-amino-2-[3-(4-furo[2,3-c]pyridin-7-yl)piperazin-1-yl]propylthio]-5,6-
 dimethyl-3H-thieno[2,3-d]pyrimidin-4-one was obtained.

30

¹H-NMR(CDCl₃)δ:7.95(d,J=5.4Hz,1H),7.60(d,J=2.3Hz,1H),
 6.96(d,J=5.4Hz,1H),6.72(d,J=1.9Hz,1H),4.77(s,2H),
 3.19(t,J=7.3Hz,4H),2.65(t,J=5.0Hz,4H),2.57(t,J=0.8Hz,3H),
 2.36(d,J=0.8Hz,3H),2.00(q,J=7.3Hz,1H)

35

Mass,m/e:470(M⁺),147(base)

Example 1-47

In the manner similar to Example 1-1,
 3-amino-2-[3-(4-furo[3,2-c]pyridin-4-yl)piperazin-1-yl]propylthiol-5,6-
 5 dimethyl-3H-thieno[2,3-d]pyrimidin-4-one was obtained.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.04(d, J=5.8Hz, 1H), 7.53(d, J=2.3Hz, 1H),
 6.94(dd, J=0.8Hz, 5.8Hz, 1H), 6.82(dd, J=1.2Hz, 2.3Hz, 1H),
 4.77(s, 2H), 3.76(t, J=5.0Hz, 4H), 3.19(t, J=7.3Hz, 2H),
 10 2.65(t, J=5.0Hz, 4H), 2.57(t, J=7.3Hz, 2H), 2.45(s, 3H), 2.36(s, 3H),
 2.05~1.96(m, 2H)
 Mass, m/e: 470(M^+), 147(base)

Example 1-48

15 In the manner similar to Example 1-1,
 3-amino-2-[3-[4-(6-methoxyisoquinolin-1-yl)piperazin-1-yl]-
 propylthiol-5,6-dimethyl-3H-thieno[2,3-d]pyrimidin-4-one was
 obtained.

20 $^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.09(d, J=5.8Hz, 1H), 8.00(d, J=9.3Hz, 1H),
 7.16~7.10(m, 2H), 7.02(d, J=2.3Hz, 1H), 4.78(s, 2H), 3.93(s, 3H),
 3.45(br s, 4H), 3.20(t, J=7.3Hz, 2H), 2.76(br s, 4H),
 2.63(t, J=6.9Hz, 2H), 2.44(s, 3H), 2.35(s, 3H), 2.03~2.00(m, 1H)
 Mass, m/e: 510(M^+), 187(base)

25

Example 1-49

In the manner similar to Example 1-1,
 3-amino-2-[3-[4-(6-methoxyisoquinolin-1-yl)piperazin-1-yl]-
 propylthiol-5,6,7,8-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyrimidin-4-
 30 one was obtained.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.09(d, J=6.0Hz, 1H), 7.99(d, J=9.3Hz, 1H),
 7.16(d, J=5.7Hz, 1H), 7.12(dd, J=2.7Hz, 9.3Hz, 1H),
 7.02(d, J=2.3Hz, 1H), 4.78(s, 2H), 3.93(s, 3H), 3.45(br s, 4H),
 35 3.22~3.18(m, 2H), 2.98~2.96(m, 2H), 2.77(br s, 4H),

2.73(t, J=5.8Hz, 2H), 2.66~2.62(m, 2H), 2.05~2.00(m, 2H),
 1.88~1.75(m, 4H)
 Mass, m/e: 536(M⁺), 187(base)

5 Example 1-50

In the manner similar to Example 1-1,
 3-amino-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylthio]-5,6,7,8-
 tetrahydro-3H-quinazolin-4-one was obtained.

10 ¹H-NMR(CDCl₃)δ: 7.89(d, J=9.0Hz, 1H), 7.70(d, J=8.3Hz, 1H),
 7.59(d, J=7.9Hz, 1H), 7.53(ddd, J=1.6Hz, 7.0Hz, 8.7Hz, 1H),
 7.24~7.20(m, 1H), 6.98(d, J=8.3Hz, 1H), 4.80(s, 2H),
 3.77(t, J=4.8Hz, 4H), 3.14(t, J=7.4Hz, 4H), 2.62~2.60(m, 4H),
 2.58~2.45(m, 6H), 1.99~1.95(m, 2H), 1.80~1.72(m, 4H)
 15 Mass, m/e: 450(M⁺), 157(base)

Example 1-51

In the manner similar to Example 1-1,
 3-amino-2-[3-[4-(4-methylquinolin-2-yl)piperazin-1-yl]propylthio]-
 20 5,6,7,8-tetrahydro-3H-quinazolin-4-one was obtained.

¹H-NMR(CDCl₃)δ: 7.77(m, 1H), 7.70(d, J=8.1Hz, 1H),
 7.53(ddd, J=1.5Hz, 7.0Hz, 8.4Hz, 1H), 7.27~7.23(m, 1H),
 6.84(d, J=0.7Hz, 1H), 4.80(s, 2H), 3.76(t, J=5.1Hz, 4H),
 25 3.16~3.12(m, 2H), 2.64~2.61(m, 4H), 2.60~2.49(m, 6H),
 1.97(q, J=7.3Hz, 2H), 1.81~1.63(m, 4H)
 Mass, m/e: 464(M⁺), 171(base)

Example 1-52

30 In the manner similar to Example 1-1,
 3-amino-2-[3-[4-(3-chloroisoquinolin-1-yl)piperazin-1-yl]propylthio]-
 5,6-dimethyl-3H-thieno[2,3-d]pyrimidin-4-one was obtained.

¹H-NMR(CDCl₃)δ: 8.01(d, J=8.1Hz, 1H), 7.65(d, J=8.1Hz, 1H),
 35 7.58(dt, J=0.8Hz, 6.6Hz, 1H), 7.45(ddd, J=1.2Hz, 6.9Hz, 8.1Hz, 1H),

7.25~7.23(m,1H),4.78(s,2H),3.53(br s,4H),3.18(t,J=7.3Hz,2H),
 2.75(br s,4H),2.63(t,J=7.3Hz,2H),2.43(s,3H),2.34(s,3H),
 2.00(q,J=7.3Hz,2H)
 Mass,m/e:514(M⁺),128(base)

5

Example 1-53

In the manner similar to Example 1-1,
 3-amino-2-[3-[4-(3-chloroisoquinolin-1-yl)piperazin-1-yl]propylthio]-
 5,6,7,8-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyrimidin-4-one was
 10 obtained.

¹H-NMR(CDCl₃)δ:8.99(d,J=8.5Hz,1H),7.65(d,J=7.0Hz,1H),
 7.59(dt,J=1.2Hz,6.9Hz,1H),7.45(ddd,J=1.5Hz,6.9Hz,8.5Hz,1H),
 7.24~7.22(m,1H),4.78(s,2H),3.59(br s,4H),3.19(t,J=7.3Hz,2H),
 15 2.97~2.90(m,2H),2.81(br s,4H),2.72~2.69(m,2H),
 2.06~2.03(m,2H),1.87~1.82(m,2H)
 Mass,m/e:128(base)

Example 1-54

20 In the manner similar to Example 1-1,
 3-amino-5,6-dimethyl-2-[3-[4-(3-methylquinoxalin-2-yl)piperazin-
 1-yl]propylthio]-3H-thieno[2,3-d]pyrimidin-4-one was obtained.

¹H-NMR(CDCl₃)δ:7.88(dd,J=1.1Hz,8.4Hz,2H),
 25 7.82(dd,J=1.1Hz,8.4Hz,2H),
 7.57(ddd,J=1.1Hz,6.9Hz,8.4Hz,1H),
 7.50(ddd,J=1.1Hz,6.9Hz,8.4Hz,1H),4.78(s,2H),
 3.39~3.48(m,4H),3.20(t,J=7.0Hz,2H),2.71(s,3H),
 2.68~2.73(m,4H),2.57~2.63(m,2H),2.45(s,3H),2.36(s,3H),
 30 1.94~2.08(m,2H)
 Mass,m/e:495(M⁺),268(base),128

Example 1-55

In the manner similar to Example 1-1,
 35 3-amino-2-[3-[4-(3-methylquinoxalin-2-yl)piperazin-1-yl]propylthio]-

5,6,7,8-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyrimidin-4-one was obtained.

¹H-NMR(CDCl₃)δ:7.88(dd,J=1.1Hz,8.1Hz,1H),
 5 7.82(dd,J=1.1Hz,8.1Hz,1H),
 7.58(ddd,J=1.1Hz,6.9Hz,8.1Hz,1H),
 7.51(ddd,J=1.1Hz,6.9Hz,8.1Hz,1H),4.77(s,2H),
 3.38~3.49(m,4H),3.20(t,J=7.1Hz,2H),2.93~2.99(m,8H),
 2.00(q,J=7.1Hz,2H),1.79~1.93(m,4H)
 10 Mass,m/e:521(M⁺),349,294,128(base)

Example 1-56

In the manner similar to Example 1-1,
 3-amino-5,6-dimethyl-2-[3-[4-(3-phenylquinoxalin-2-yl)piperazin-1-
 15 yl]propylthio]-3H-thieno[2,3-d]pyrimidin-4-one was obtained.

¹H-NMR(CDCl₃)δ:7.96~8.01(m,2H),
 7.84(dd,J=1.5Hz,8.4Hz,1H),
 7.60(ddd,J=1.1Hz,6.9Hz,8.1Hz,1H),7.41~7.52(m,5H),
 20 4.75(s,2H),3.29~3.37(m,4H),3.14(t,J=7.0Hz,2H),
 2.47~2.53(m,4H),2.43(s,3H),2.35(s,3H),1.91(q,J=7.0Hz,2H),
 1.24(t,J=7.0Hz,2H)
 Mass,m/e:557(M⁺),128(base)

Example 1-57

In the manner similar to Example 1-1,
 3-amino-4-oxo-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylthio]-3,4-
 dihydroquinazoline-7-carboxylic acid was obtained.

¹H-NMR(DMSO-d₆)δ:8.05~7.99(m,2H),7.72~7.66(m,2H),
 30 7.57~7.47(m,3H),7.24~7.18(m,2H),5.79(br s,2H),
 3.68(br s,4H),3.17~3.13(m,2H),2.81~2.77(m,2H),
 2.54~2.52(m,4H),1.90~1.83(m,2H)
 Mass,m/e:490(M⁺),157(base)

Example 1-58

In 10 ml of tert-butanol, 250 mg of 3-amino-4-oxo-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylthio]-3,4-dihydroquinazolin-7-carboxylic acid as synthesized in Example 1-57 was dissolved, to which 52 mg of triethylamine, and further 147 mg of DPPA, were added by the order stated. This mixture was heated under reflux for an overnight. Distilling the solvent off under reduced pressure, the residue was purified on silica gel column chromatography (chloroform : methanol = 50:1). The purified product was added to 8 ml of 4N hydrochloric acid-dioxane solution, stirred for an hour, and an excessive amount of triethylamine was added. Distilling the solvent off under reduced pressure, the residue was purified on silica gel column chromatography (chloroform : methanol = 50:1) to provide 20 mg (8%) of 3,7-diamino-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylthio]-3H-quinazolin-4-one.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.02(d, J=9.2Hz, 1H), 7.72~7.67(m, 2H), 7.56~7.49(m, 2H), 7.25~7.19(m, 2H), 6.65~6.62(m, 1H), 6.50(d, J=2.2Hz, 1H), 6.03(br s, 2H), 5.51(br s, 2H), 3.70(br s, 2H), 3.05(t, J=7.0Hz, 2H), 2.53~2.45(m, 6H), 1.98~1.87(m, 2H)
Mass, m/e: 461(M^+), 157(base)

Example 1-59

To 6 ml of 4N-hydrochloric acid-dioxane solution, 100 mg of 3-amino-7-tert-butoxycarbonyl-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylthio]-3,4,5,6,7,8-hexahydro-4-oxa-9-thia-1,3,7-triaza-9H-fluorene as synthesized in Example 1-13 was added and stirred for 2.5 hours. Distilling the solvent off under reduced pressure, 105 mg (100%) of 3-amino-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylthio]-3,4,5,6,7,8-hexahydro-4-oxa-9-thia-1,3,7-triaza-9H-fluorene trihydrochloride was obtained.

$^1\text{H-NMR}(\text{DMSO}-d_6)\delta$: 9.82(br s, 1H), 8.46(d, J=9.5Hz, 1H), 8.32(br s, 1H), 7.93(d, J=7.7Hz, 1H), 7.78(m, 1H),

7.58(d, J=9.2Hz, 1H), 7.50(m, 1H), 4.87(d, J=8.2Hz, 2H),
 4.33(br s, 2H), 4.20~3.85(m, 4H), 3.70(d, J=5.4Hz, 2H),
 3.39(br s, 2H), 3.26(br s, 2H), 3.17~3.13(m, 4H), 2.23~2.16(m, 2H)
 Mass, m/e: 507(M⁺), 157(base)

5

Example 1-60

In the manner similar to Example 1-59,
 3-amino-2-[3-(4-benzothiazol-2-ylpiperazin-1-yl)propylthio]-
 3,4,5,6,7,8-hexahydro-4-oxa-9-thia-1,3,7-triaza-9H-fluorene was
 10 obtained from 3-amino-7-tert-butoxycarbonyl-2-[3-(4-benzothiazol-
 2-ylpiperazin-1-yl)propylthio]-3,4,5,6,7,8-hexahydro-4-oxa-9-thia-
 1,3,7-triaza-9H-fluorene which was synthesized in Example 1-20.

¹H-NMR(CDCl₃) δ: 7.60(dd, J=1.0Hz, 7.9Hz, 1H),
 15 7.56(d, J=7.6Hz, 1H), 7.32~7.28(m, 1H), 7.10~7.06(m, 1H),
 4.79(s, 2H), 4.03~4.02(m, 2H), 3.70~3.67(m, 4H),
 3.21~3.12(m, 4H), 3.02~3.00(m, 2H), 2.62(t, J=5.1Hz, 4H),
 2.57(t, J=7.0Hz, 2H), 1.98(q, J=7.3Hz, 2H)
 Mass, m/e: 513(M⁺), 163(base)

20

Example 1-61

First, in the manner similar to Example 1-1,
 3-amino-7-tert-butoxycarbonyl-2-[3-[4-(4-methylquinolin-2-yl)-
 piperazin-1-yl]propylthio]-3,4,5,6,7,8-hexahydro-4-oxa-9-thia-1,3,7-
 25 triza-9H-fluorene was obtained. Then, in the manner similar to
 Example 1-59, 3-amino-2-[3-[4-(4-methylquinolin-2-yl)piperazin-
 1-yl]propylthio]-3,4,5,6,7,8-hexahydro-4-oxa-9-thia-1,3,7-triaza-9H-
 fluorene trihydrochloride was prepared.

30 ¹H-NMR(DMSO-d₆) δ: 8.05~7.05(m, 5H), 4.34(br s, 4H),
 3.71~3.15(m, 6H), 2.69(m, 4H), 2.51~2.46(m, 7H), 2.20(m, 2H)
 Mass, m/e: 521(M⁺), 171(base)

Example 1-62

35 To 10 ml of tetrahydrofuran, 203 mg of 3-amino-2-[3-(4-

quinolin-2-ylpiperazin-1-yl)propylthio]-3,4,5,6,7,8-hexahydro-4-oxa-9-thia-1,3,7-triaza-9H-fluorene trihydrochloride as synthesized in Example 1-59 was added and into which 133 mg of triethylamine was dropped. Acetyl chloride was added to the mixture under cooling with ice, followed by 30 minutes' stirring and distillation under reduced pressure. The residue was purified on silica gel column chromatography (chloroform : methanol = 25:1) to provide 150 mg (83%) of 7-acetyl-3-amino-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylthio]-3,4,5,6,7,8-hexahydro-4-oxa-9-thia-1,3,7-triaza-9H-fluorene.

¹H-NMR(CDCl₃)δ: 7.99(d, J=8.9Hz, 1H), 7.70(d, J=8.5Hz, 1H), 7.59(d, J=7.7Hz, 1H), 7.55~7.51(m, 1H), 7.24~7.21(m, 1H), 6.99(d, J=9.2Hz, 1H), 4.78(br s, 4H), 3.79(t, J=4.6Hz, 4H), 3.75(d, J=5.8Hz, 2H), 3.22~3.19(m, 2H), 3.15~3.07(m, 2H), 2.67(t, J=4.6Hz, 4H), 2.58~2.55(m, 2H), 2.21(s, 3H), 2.04~1.96(m, 2H)
Mass, m/e: 549(M⁺), 157(base)

20 Example 1-63

To 10 ml of tetrahydrofuran, 310 mg of 3-amino-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylthio]-3,4,5,6,7,8-hexahydro-4-oxa-9-thia-1,3,7-triaza-9H-fluorene trihydrochloride as synthesized in Example 1-59 was added and further 50 mg of ethyl iodide was added. Into this mixture 200 mg of triethylamine was dropped, followed by 3 days' stirring at room temperature. Distilling the solvent off under reduced pressure, the residue was purified on silica gel column chromatography (chloroform : methanol = 10:1) to provide 100 mg (37%) of 3-amino-7-ethyl-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylthio]-3,4,5,6,7,8-hexahydro-4-oxa-9-thia-1,3,7-triaza-9H-fluorene.

¹H-NMR(CDCl₃)δ: 7.87(d, J=8.9Hz, 1H), 7.69(d, J=8.5Hz, 1H), 7.59~7.57(m, 1H), 7.54~7.50(m, 1H), 7.21(ddd, J=1.2Hz, 7.0Hz, 8.5Hz, 1H), 6.97(d, J=9.3Hz, 1H),

4.87(s,2H),3.79~3.76(m,4H),3.65(br s,2H),3.18(t,J=7.3Hz,2H),
 3.08(t,J=5.8Hz,2H),2.81(t,J=5.8Hz,2H),2.67~2.60(m,6H),
 2.55(t,J=7.0Hz,2H),2.02~1.95(m,2H),1.20(t,J=7.3Hz,3H)
 Mass,m/e:535(M⁺),157(base)

5

Example 2: Syntheses of compounds of the formula (I) in which X¹
 stands for hydrogen and Y stands for sulfur

Example 2-1

In 3 ml of ethanol, 75 mg of potassium 5,6-dimethyl-4-oxo-3,4-
 10 dihydrothieno[2,3-d]pyrimidine-2-thiolate, which was prepared from
 ethyl 2-amino-4,5-dimethylthiophene-3-carboxylate, and 87 mg of
 2-[4-(3-chloropropyl)piperazin-1-yl]pyridine were heated under reflux
 for 5 hours. Cooling the reaction system off, chloroform was added,
 followed by washing with saturated brine. The organic layer was
 15 dried over anhydrous magnesium sulfate and the solvent was
 distilled off under reduced pressure. The residue was purified on
 silica gel column chromatography (chloroform : methanol = 100:1) to
 provide 93 mg (75%) of 5,6-dimethyl-2-
 [3-(4-pyridin-2-ylpiperazin-1-yl)propylthio]-3H-thieno[2,3-d]-
 20 pyrimidin-4-one.

melting point: 209.0 – 209.4°C

¹H-NMR(CDCl₃)δ:8.20~8.18(m,1H),
 7.47(ddd,J=1.9Hz,7.1Hz,8.8Hz,1H),6.65(d,J=8.6Hz,1H),
 25 6.61(dd,J=5.0Hz,7.1Hz,1H),3.63(t,J=5.1Hz,4H),
 3.28(t,J=6.9Hz,2H),2.63(t,J=5.1Hz,4H),2.59(d,J=6.7Hz,2H),
 2.43(s,3H),2.35(s,3H),2.01(q,J=6.8Hz,2H)
 IR(KBr)ν_{max}:3468,1650,1590cm⁻¹
 Mass,m/e:415(M⁺),107(base)

30

Example 2-2

In the manner similar to Example 2-1,
 2-[3-(4-pyridin-2-ylpiperazin-1-yl)propylthio]-5,6,7,8-tetrahydro-3H-
 benzo[4,5]thieno[2,3-d]pyrimidin-4-one was obtained.

35

melting point: 190.2 – 191.6°C

¹H-NMR(CDCl₃)δ: 8.19(ddd, J=0.8Hz, 2.0Hz, 4.9Hz, 1H),
 7.47(ddd, J=2.0Hz, 7.1Hz, 8.6Hz, 1H), 6.65(d, J=8.6Hz, 1H),
 6.61(ddd, J=0.8Hz, 4.9Hz, 7.1Hz, 1H), 3.64(t, J=6.9Hz, 4H),
 3.29(t, J=6.9Hz, 2H), 2.99~2.95(m, 2H), 2.76~2.72(m, 2H),
 2.63(t, J=5.0Hz, 4H), 2.59(d, J=6.8Hz, 2H), 1.90~1.79(m, 4H)
 IR(KBr)ν_{max}: 2932, 1666, 1594 cm⁻¹
 Mass, m/e: 441(M⁺), 107(base)

10 Example 2-3

In the manner similar to Example 2-1,
 5-methyl-4-oxo-2-[3-(4-pyridin-2-ylpiperazin-1-yl)propylthio]-3,4-
 dihydrothieno[2,3-d]pyrimidine-6-carboxylic acid ethyl ester was
 obtained.

15

melting point: 160.1 – 161.8°C
¹H-NMR(CDCl₃)δ: 8.19~8.17(m, 1H), 7.48~7.45(m, 1H),
 6.65(d, J=8.6Hz, 1H), 6.62(dd, J=4.9Hz, 7.1Hz, 1H),
 4.34(q, J=7.1Hz, 2H), 3.66~3.63(m, 4H), 3.27~3.20(m, 2H),
 2.84(s, 3H), 2.73(t, J=5.1Hz, 4H), 2.68(t, J=7.0Hz, 2H),
 2.12~2.06(m, 2H), 1.39(t, J=7.1Hz, 3H)
 IR(KBr)ν_{max}: 3452, 2928, 1710, 1656, 1594 cm⁻¹
 Mass, m/e: 473(M⁺), 107(base)

25 Example 2-4

In the manner similar to Example 2-1,
 5,6-dimethyl-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylthio]-3H-
 thieno[2,3-d]pyrimidin-4-one was obtained.

30

melting point: 224.8 – 225.9°C
¹H-NMR(CDCl₃)δ: 7.88(d, J=8.8Hz, 1H), 7.70(d, J=8.6Hz, 1H),
 7.59(dd, J=1.2Hz, 8.0Hz, 1H), 7.54~7.50(m, 1H),
 7.22(ddd, J=1.2Hz, 6.9Hz, 8.0Hz, 1H), 6.98(d, J=9.2Hz, 1H),
 3.89~3.80(m, 4H), 3.29(t, J=6.9Hz, 2H), 2.67(t, J=4.9Hz, 4H),
 2.62(t, J=6.8Hz, 2H), 2.43(d, J=0.8Hz, 3H), 2.43(d, J=0.8Hz, 3H),

35

2.08~1.98(m,2H)

IR(KBr) ν_{max} :3056,2916,1678,1616,1552 cm^{-1}

Mass,m/e:465(M^+),157(base)

5 Example 2-5

In the manner similar to Example 2-1,
2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylthio]-5,6,7,8-tetrahydro-
3H-benzo-[4,5]thieno[2,3-d]pyrimidin-4-one was obtained.

10 $^1\text{H-NMR}(\text{CDCl}_3)\delta$:7.89(d,J=9.0Hz,1H),7.70(d,J=8.0Hz,1H),
7.60(d,J=7.8Hz,1H),7.55~7.51(m,1H),7.24~7.18(m,1H),
6.99(d,J=9.0Hz,1H),3.89(br s,4H),3.30(t,J=6.8Hz,2H),
3.01~2.92(m,2H),2.78~2.70(m,2H),2.66(br s,4H),
2.68~2.58(m,2H),1.89~1.78(m,2H),1.59~1.50(m,2H)
15 IR(KBr) ν_{max} :3056,2932,1678,1616,1604,1550,1504 cm^{-1}
Mass,m/e:491(M^+),157(base)

Example 2-6

In the manner similar to Example 2-1,
20 5-methyl-4-oxo-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylthio]-3,4-
dihydrothieno[2,3-d]pyrimidine-6-carboxylic acid ethyl ester was
obtained.

melting point: 200.1 – 201.4°C

25 $^1\text{H-NMR}(\text{CDCl}_3)\delta$:7.89(d,J=9.1Hz,1H),7.69(d,J=7.8Hz,1H),
7.59(dd,J=1.1Hz,7.9Hz,1H),7.53~7.51(m,1H),7.23~7.21(m,1H),
6.98(dd,J=2.7Hz,9.2Hz,1H),4.34(q,J=7.1Hz,2H),
3.86~3.85(m,4H),3.27(t,J=6.2Hz,2H),2.84(s,3H),
2.78~2.76(m,4H),2.70(t,J=7.0Hz,2H),2.12~2.11(m,2H),
30 1.39(t,J=7.1Hz,3H)
IR(KBr) ν_{max} :3464,3048,2936,1712,1662,1604 cm^{-1}
Mass,m/e:523(M^+),157(base)

Example 2-7

35 In the manner similar to Example 2-1,

2-[3-(4-benzothiazol-2-ylpiperazin-1-yl)propylthio]-3H-quinazolin-4-one was obtained.

¹H-NMR(DMSO-d₆)δ:8.04(dd,J=1.5Hz,8.1Hz,1H),
 7.78~7.74(m,1H),7.51(d,J=8.1Hz,1H),7.45(d,J=8.1Hz,1H),
 7.43~7.39(m,1H),7.29~7.27(m,1H),7.08~7.05(m,1H),
 3.59(t,J=5.0Hz,4H),3.27~3.25(m,2H),2.54(t,J=5.0Hz,4H),
 2.51~2.49(m,2H),1.95~1.88(m,2H)
 Mass,m/e:437(M⁺),163,109(base)

Example 2-8

In the manner similar to Example 2-1,
 2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylthio]-3H-quinazolin-4-one
 was obtained.

¹H-NMR(CDCl₃)δ:8.16(dd,J=1.5Hz,8.5Hz,1H),
 7.88(d,J=8.1Hz,1H),7.70~7.66(m,2H),7.60~7.50(m,3H),
 7.35(ddd,J=1.1Hz,6.9Hz,8.1Hz,1H),
 7.21(ddd,J=0.8Hz,6.9Hz,8.1Hz,1H),6.98(d,J=9.2Hz,1H),
 3.88(t,J=5.0Hz,4H),3.34(t,J=7.0Hz,2H),2.68~2.63(m,6H),
 2.07~2.04(m,2H)
 Mass,m/e:431(M⁺),157(base)

Example 2-9

In the manner similar to Example 2-1,
 5,6-dimethyl-2-[3-(4-pyrrolo[1,2-a]quinoxalin-4-ylpiperazin-1-yl)-
 propylthio]-3H-thieno[2,3-d]pyrimidin-4-one was obtained.

¹H-NMR(CDCl₃)δ:7.87(dd,J=1.4Hz,2.8Hz,1H),
 7.79~7.76(m,1H),7.70~7.69(m,2H),7.36~7.28(m,2H),
 6.82(dd,J=1.4Hz,3.9Hz,1H),6.79~6.78(m,1H),
 3.85(t,J=4.9Hz,4H),3.29(t,J=7.2Hz,2H),2.72(t,J=4.9Hz,4H),
 2.63~2.60(m,2H),2.42(s,3H),2.37(s,3H),2.05~2.01(m,2H)
 IR(KBr)ν_{max}:2920,2824,1668,1518cm⁻¹
 Mass,m/e:504(M⁺),196(base)

Example 2-10

In the manner similar to Example 2-1,

2-[3-(4-pyrrolo[1,2-a]quinoxalin-4-ylpiperazin-1-yl)propylthio]-5,6,7,8-
5 tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyrimidin-4-one was obtained.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.87(dd, $J=1.2\text{Hz}, 2.0\text{Hz}$, 1H),
7.79~7.76(m, 1H), 7.69~7.67(m, 1H), 7.35~7.28(m, 1H),
6.83~6.82(m, 1H), 6.78(dd, $J=2.8\text{Hz}, 4.0\text{Hz}$, 1H), 3.86~3.84(m, 4H),
10 3.29(t, $J=7.3\text{Hz}$, 2H), 2.94($J=5.9\text{Hz}$, 2H), 2.76~2.71(m, 6H),
2.63~2.60(m, 2H), 1.89~1.82(m, 2H)
IR(KBr) ν_{max} : 2936, 1664, 1518 cm^{-1}
Mass, m/e : 530(M^+), 196(base)

15 Example 2-11

In the manner similar to Example 2-1,

2-[3-(4-benzothiazol-2-ylpiperazin-1-yl)propylthio]-5,6-dimethyl-3H-
thieno[2,3-d]pyrimidin-4-one was obtained.

20 Mass, m/e : 471(M^+), 163(base)

Example 2-12

In the manner similar to Example 2-1,

2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylthio]-3H-thieno[3,2-d]-
25 pyrimidin-4-one was obtained.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.89(d, $J=9.2\text{Hz}$, 1H), 7.73(d, $J=5.1\text{Hz}$, 1H),
7.70(d, $J=8.1\text{Hz}$, 1H), 7.59(d, $J=7.7\text{Hz}$, 1H), 7.55~7.51(m, 1H),
7.26~7.20(m, 1H), 6.98(d, $J=9.2\text{Hz}$, 1H), 3.91(t, $J=4.8\text{Hz}$, 4H),
30 3.34~3.31(m, 2H), 2.71~2.65(m, 6H), 2.08~2.02(m, 2H)
Mass, m/e : 437(M^+), 157(base)

Example 2-13

In the manner similar to Example 2-1,

35 5,6-dimethyl-2-[4-(4-quinolin-2-yl-piperazin-1-yl)but-2-enylthio]-3H-

thieno[2,3-d]pyrimidin-4-one was obtained.

¹H-NMR(CDCl₃)δ:7.87(d,J=9.2Hz,1H),7.69(d,J=8.6Hz,1H),
7.60~7.57(m,1H),7.54~7.50(m,1H),7.23~7.20(m,1H),
5 6.94(d,J=8.9Hz,1H),5.88(q,J=6.4Hz,1H),5.78(q,J=6.7Hz,1H),
3.89(d,J=6.7Hz,1H),3.71(t,J=5.1Hz,4H),3.05(d,J=6.4Hz,1H),
2.54(t,J=5.1Hz,4H),2.46(s,3H),2.35(s,3H)
Mass,m/e:477(M⁺),157(base)

10 Example 2-14

In the manner similar to Example 2-1,
6-propyl-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylthio]-3H-pyrimidin-
4-one was obtained.

15 ¹H-NMR(CDCl₃)δ:7.89(d,J=9.2Hz,1H),7.69(d,J=9.4Hz,1H),
7.59(d,J=8.1Hz,1H),7.55~7.51(m,1H),7.24~7.20(m,1H),
6.98(d,J=9.2Hz,1H),6.01(s,1H),3.83(t,J=4.8Hz,4H),
3.25(t,J=7.0Hz,2H),2.62(t,J=4.8Hz,4H),2.59~2.56(m,2H),
1.99(q,J=6.9Hz,2H),1.68(q,J=7.3Hz,2H),0.97(t,J=7.3Hz,3H)
20 Mass,m/e:423(M⁺),157(base)

Example 2-15

In the manner similar to Example 2-1,
5,6-dimethyl-2-[3-[4-(3-methylquinoxalin-2-yl)piperazin-1-yl]-
25 propylsulfanyl]-3H-thieno[2,3-d]pyrimidin-4-one was obtained.

¹H-NMR(CDCl₃)δ:7.88(dd,J=1.1Hz,8.1Hz,1H),
7.81(dd,J=1.1Hz,8.1Hz,1H),
7.57(ddd,J=1.1Hz,6.9Hz,8.1Hz,1H),
30 7.51(ddd,J=1.1Hz,6.9Hz,8.1Hz,1H),3.49(t,J=4.4Hz,4H),
3.29(t,J=7.0Hz,2H),2.75(t,J=4.4Hz,4H),2.71(s,3H),
2.65(t,J=7.0Hz,2H),2.42(s,3H),2.33(s,3H),2.04(q,J=7.0Hz,2H)
Mass,m/e:480(M⁺),321,253(base)

35 Example 2-16

To 1N-aqueous sodium hydroxide solution, 105 mg of ethyl 5-methyl-4-oxo-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylthio]-3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxylate which was synthesized in Example 2-6 was added and stirred at 70°C – 100°C for an hour.

- 5 The reaction mixture was cooled and washed with chloroform. The aqueous layer was neutralized with 2N-hydrochloric acid, and the precipitate was recovered by filtration and dried to provide 100 mg (100%) of 5-methyl-4-oxo-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylthio]-3,4-dihydrothieno[2,3-d]-
10 pyrimidine-6-carboxylic acid.

¹H-NMR(DMSO-d₆)δ:8.16(d,J=8.1Hz,1H),7.76(d,J=8.1Hz,1H),
7.66~7.75(m,1H),7.60~7.59(m,1H),7.36~7.29(m,2H),
4.65~4.64(m,4H),3.64~3.62(m,4H),3.39~3.27(m,7H),
15 2.19~2.16(m,2H)
IR(KBr)ν_{max}:3432,1648,1536cm⁻¹
Mass,m/e:451(M⁺),157(base)

Example 2-17

- 20 In the manner similar to Example 2-16,
5-methyl-4-oxo-2-[3-(4-pyridin-2-ylpiperazin-1-yl)propylthio]-3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxylic acid was obtained from
5-methyl-4-oxo-2-[3-(4-pyridin-2-ylpiperazin-1-yl)propylthio]-3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxylic acid ethyl ester which
25 was synthesized in Example 2-3.

¹H-NMR(DMSO-d₆)δ:8.11~8.09(m,1H),
7.52(ddd,J=1.8Hz,7.0Hz,8.8Hz,1H),6.81(d,J=8.4Hz,1H),
6.64~6.61(m,1H),3.53~5.49(m,4H),3.21~3.20(m,2H),
30 2.76(s,3H),2.66~2.54(m,4H),2.52~2.47(m,4H),1.92~1.85(m,2H)
IR(KBr)ν_{max}:3464,2928,1664,1534cm⁻¹
Mass,m/e:445(M⁺),107(base)

Example 2-18

- 35 In 20 ml of tert-butanol, 470 Milligrams of 5-methyl-4-oxo-

2-[3-(4-pyridin-2-ylpiperazin-1-yl)propylthio]-3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxylic acid as synthesized in Example 2-17 was dissolved to which 107 mg of triethylamine and 305 mg of DPPA were added by the order stated, followed by 9 hours' heating under reflux.

5 Distilling the solvent off under reduced pressure, the residue was purified on silica gel column chromatography (chloroform : methanol = 50:1). The purified product was added to 6 ml of 4N-hydrochloric acid-dioxane solution, stirred for an overnight and from which the solvent was distilled off under reduced pressure. To the residue

10 chloroform was added, followed by washing with saturated aqueous sodium hydrogencarbonate solution, drying over anhydrous magnesium sulfate and removal of the solvent by distillation under reduced pressure. The residue was purified on silica gel column chromatography (chloroform : methanol = 25:1) to provide 78 mg

15 (18%) of 6-amino-5-methyl-2-[3-(4-pyridin-2-ylpiperazin-1-yl)propylthio]-3H-thieno[2,3-d]pyrimidin-4-one.

Example 2-19

In the manner similar to Example 2-18,

20 6-amino-5-methyl-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylthio]-3H-thieno[2,3-d]pyrimidin-4-one was obtained from 5-methyl-4-oxo-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylthio]-3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxylic acid which was synthesized in Example 2-16.

25 ¹H-NMR(CD₃OD)δ:8.02(d,J=9.0Hz,1H),7.69(d,J=8.1Hz,1H),
7.57~7.50(m,2H),7.24~7.21(m,2H),
5.45(br s,1H),3.34~3.28(m,6H),2.53~2.48(m,4H),
2.44(t,J=6.6Hz,2H),1.89~1.81(m,2H)

30 Mass,m/e:466(M⁺),157(base)

Example 2-20

In the manner similar to Example 2-1,

2-[3-[4-(4-methylquinolin-2-yl)piperazin-1-yl]propylthio]-3,4,5,6,7,8-hexahydro-4-oxo-9-thia-1,3,7-triaza-9H-fluorene trihydrochloride was

35

obtained.

¹H-NMR(DMSO-d₆)δ:9.62(br s,1H),8.13(d,J=8.1Hz,1H),
 7.78~7.76(m,1H),7.54~7.51(m,3H),4.83(br s,2H),4.33(s,2H),
 5 3.71~3.68(m,4H),3.25~3.24(m,2H),3.13~3.12(m,2H),2.69(s,7H),
 2.24~2.19(m,2H)
 Mass,m/e:506(M⁺),171(base)

Example 2-21

10 In the manner similar to Example 2-1,
 2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylthio-3,4,5,6,7,8-hexahydro-4-
 oxa-9-thia-1,3,7-triaza-9H-fluorene trihydrochloride was obtained.

¹H-NMR(DMSO-d₆)δ:11.86(br s,1H),9.89(br s,1H),
 15 8.50(d,J=9.6Hz,1H),8.42(d,J=8.9Hz,1H),7.95(d,J=8.1Hz,1H),
 7.80(t,J=7.3Hz,1H),7.61(d,J=9.6Hz,1H),7.53(t,J=7.3Hz,1H),
 4.91(br s,2H),4.32(br s,2H),3.93~3.87(m,2H),3.36~3.24(m,6H),
 3.17~3.13(m,2H),2.51~2.49(m,2H),2.21(q,J=7.3Hz,2H)
 Mass,m/e:492(M⁺),157(base)

20

Example 3: Syntheses of compounds of the formula (I) in which X¹
 stands for hydrogen and Y is direct bond

Example 3-1

Step 3-1-A:

25 To 10 ml of 4N-hydrochloric acid-dioxane solution, 996 mg of
 ethyl 2-amino-4,5-dimethylthiophene-3-carboxylate was added and
 into which 972 mg of 5-bromopentanenitrile was dropped. After 6
 hours' stirring at room temperature, the reaction mixture was poured
 into ice water, neutralized with 25% ammonia water, and the
 30 precipitate was recovered by filtration. The precipitate was washed
 with chloroform-ethanol mixed solvent and dried to provide 750 mg
 (48%) of 2-(4-bromobutyl)-5,6-dimethyl-3H-
 thieno[2,3-c]pyrimidin-4-one.

35 ¹H-NMR(CDCl₃):3.45(t,J=6.3Hz,2H),2.77(t,J=6.3Hz,2H),

2.45(d, J=0.6Hz, 3H), 2.01(s, 3H), 2.00~1.98(m, 4H)
 Mass, m/e: 314(M⁺), 235(base)

Step 3-1-B:

5 To 10 ml of tetrahydrofuran, 124 mg of
 2-(4-bromobutyl)-5,6-dimethyl-3H-thieno [2,3-c]pyrimidin-4-one as
 prepared in Step 3-1-A and 168 mg of 2-piperazin-1-ylquinoline were
 added and heated under reflux for 2 hours. Distilling the solvent off
 under reduced pressure, the residue was purified on silica gel column
 10 chromatography (chloroform : methanol = 50:1) to provide 74 mg
 (42%) of 5,6-dimethyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3H-
 thieno[2,3-d]pyrimidin-4-one.

15 ¹H-NMR(CDCl₃)δ: 7.89(d, J=9.2Hz, 1H), 7.69(d, J=8.3Hz, 1H),
 7.59(dd, J=1.3Hz, 8.1Hz, 1H), 7.53(ddd, 1.5Hz, 6.9Hz, 9.9Hz, 1H),
 7.24~7.20(m, 1H), 6.98(d, J=9.2Hz, 1H), 3.86~3.84(m, 4H),
 2.75(t, J=7.2Hz, 2H), 2.63(t, J=5.0Hz, 4H), 2.51~2.48(m, 2H),
 2.47(d, J=0.6Hz, 3H), 2.38(d, J=0.6Hz, 3H), 1.91~1.87(m, 2H),
 1.72~1.64(m, 2H)
 20 IR(KBr)ν_{max}: 2924, 1664, 1594 cm⁻¹
 Mass, m/e: 447(M⁺), 157(base)

Example 3-2

25 In the manner similar to Example 3-1,
 5,6-dimethyl-2-(4-pyridin-2-ylpiperazin-1-ylmethyl)-3H-thieno-
 [2,3-d]pyrimidin-4-one was obtained.

30 ¹H-NMR(CDCl₃)δ: 9.88(br s, 1H), 8.23(dd, J=1.8Hz, 5.4Hz, 1H),
 7.53~7.48(m, 1H), 6.68~6.62(m, 2H), 3.62(t, J=4.9Hz, 4H),
 3.59(s, 2H), 2.69(t, J=5.1Hz, 4H), 2.49(d, J=0.7Hz, 3H), 2.39(s, 3H)
 Mass, m/e: 355(M⁺), 107(base)

Example 3-3

35 In the manner similar to Example 3-1,

5,6-dimethyl-2-(4-quinolin-2-ylpiperazin-1-ylmethyl)-3H-thieno[2,3-d]pyrimidin-4-one was obtained.

¹H-NMR(CDCl₃)δ:9.88(br s,1H),7.92(d,J=9.1Hz,1H),
 5 7.71(d,J=8.3Hz,1H),7.61(d,J=8.0Hz,1H),7.56~7.53(m,1H),
 7.26~7.20(m,1H),6.99(d,J=9.1Hz,1H),3.83(t,J=5.0Hz,4H),
 3.60(s,2H),2.72(t,J=5.0Hz,4H),2.50(d,J=0.6Hz,3H),2.39(s,3H)
 Mass,m/e:405(M⁺),157(base)

10 Example 3-4

In the manner similar to Example 3-1,
 5,6-dimethyl-2-(4-pyrrolo[1,2-a]quinoxalin-4-ylpiperazin-1-ylmethyl)-
 3H-thieno[2,3-d]pyrimidin-4-one was obtained.

¹H-NMR(CDCl₃)δ:9.88(br s,1H),7.83~7.82(m,1H),
 15 7.74~7.72(m,1H),7.36~7.28(m,2H),6.78~6.75(m,2H),
 3.87(t,J=4.9Hz,4H),3.63(s,2H),2.79(t,4.9Hz,4H),
 2.50(d,J=0.8Hz,3H),2.40(s,3H)
 Mass,m/e:444(M⁺),196(base)

20

Example 3-5

In the manner similar to Example 3-1,
 2-(4-pyridin-2-ylpiperazin-1-ylmethyl)-5,6,7,8-tetrahydro-3H-
 benzo[4,5]thieno[2,3-d]pyrimidin-4-one was obtained.

25

¹H-NMR(CDCl₃)δ:9.86(br s,1H),8.20~8.19(m,1H),
 7.50(ddd,J=1.8Hz,7.0Hz,8.4Hz,1H),6.67~6.64(m,2H),
 3.64~3.62(m,4H),3.59(s,2H),3.02~3.01(m,2H),
 2.78(t,J=5.9Hz,2H),2.69(t,J=5.1Hz,4H),1.92~1.81(m,4H)
 30 Mass,m/e:381(M⁺),107(base)

Example 3-6

In the manner similar to Example 3-1,
 2-(4-quinolin-2-ylpiperazin-1-ylmethyl)-5,6,7,8-tetrahydro-3H-
 35 benzo[4,5]thieno[2,3-d]pyrimidin-4-one was obtained.

¹H-NMR(CDCl₃)δ: 9.91(br s, 1H), 7.92(d, J=9.0Hz, 1H),
 7.71(d, J=8.5Hz, 1H), 7.61~7.60(m, 1H),
 7.55(ddd, J=1.4Hz, 7.1Hz, 8.5Hz, 1H), 7.27~7.23(m, 1H),
 6.99(d, J=9.3Hz, 1H), 3.38(t, J=4.9Hz, 4H), 3.62(s, 2H),
 3.03~3.02(m, 2H), 2.78~2.76(m, 2H), 2.72(t, J=4.9Hz, 4H),
 1.92~1.82(m, 4H)
 Mass, m/e: 431(M⁺), 157(base)

10 Example 3-7

In the manner similar to Example 3-1,
 2-(4-pyrrolo[1,2-a]quinoxalin-4-ylpiperazin-1-ylmethyl)-5,6,7,8-
 tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyrimidin-4-one was obtained.

15 ¹H-NMR(CDCl₃)δ: 7.84~7.83(m, 1H),
 7.74(dd, J=1.7Hz, 8.0Hz, 1H), 7.69(dd, J=1.7Hz, 7.7Hz, 1H),
 7.36~7.25(m, 2H), 6.78~6.76(m, 2H), 3.03(s, 2H),
 3.03~3.02(m, 2H), 2.80~2.78(m, 6H), 1.90~1.85(m, 4H)
 Mass, m/e: 470(M⁺), 196(base)

20

Example 3-8

In the manner similar to Example 3-1,
 2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-5,6,7,8-tetrahydro-3H-
 benzo[4,5]thieno[2,3-d]pyrimidin-4-one was obtained.

25

¹H-NMR(CDCl₃)δ: 7.88(d, J=9.2Hz, 1H), 7.69(d, J=8.6Hz, 1H),
 7.56(d, J=7.3Hz, 1H), 7.54~7.53(m, 1H), 7.23~7.21(m, 1H),
 6.97(d, J=9.2Hz, 1H), 3.85~3.83(m, 4H), 2.78~2.74(m, 2H),
 2.64~2.63(m, 4H), 2.51~2.47(m, 2H), 1.99~1.64(m, 8H)
 30 Mass, m/e: 473(M⁺), 157(base)

Example 3-9

In the manner similar to Example 3-1,
 5,6-dimethyl-2-[4-(4-pyridin-2-ylpiperazin-1-yl)butyl]-3H-
 35 thieno[2,3-d]pyrimidin-4-one was obtained.

¹H-NMR(CDCl₃)δ:8.18(dd,J=1.2Hz,4.9Hz,1H),
 7.47(ddd,J=1.8Hz,7.3Hz,9.1Hz,1H),6.64(d,J=8.8Hz,1H),
 6.62~6.60(m,1H),3.63~3.61(m,4H),2.75~2.74(m,4H),
 2.49~2.45(m,5H),2.38(s,3H),1.92~1.84(m,2H),1.70~1.62(m,2H)
 IR(KBr)ν_{max}:2836,1664,1594cm⁻¹
 Mass,m/e:397(M⁺), 107 (base)

Example 3-10

In the manner similar to Example 3-1,
 2-[4-(4-pyridin-2-ylpiperazin-1-yl)butyl]-5,6,7,8-tetrahydro-3H-
 benzo[4,5]thieno[2,3-d]pyrimidin-4-one was obtained.

melting point: 192.6 – 194.4°C
¹H-NMR(CDCl₃)δ:11.20(br s,1H),8.18(dd,J=1.2Hz,4.9Hz,1H),
 7.49~7.45(m,1H),6.64(d,J=8.8Hz,1H),6.63~6.60(m,1H),
 3.62(t,J=5.5Hz,4H),3.01~2.98(m,2H),2.78~2.73(m,4H),
 2.59(t,J=5.2Hz,4H),2.47(t,J=7.0Hz,2H),1.92~1.82(m,4H),
 1.69~1.59(m,4H)
 IR(KBr)ν_{max}:2928,1664,1954,1482cm⁻¹
 Mass,m/e:423(M⁺),107(base)

Example 3-11

In the manner similar to Example 3-1,
 5,6-dimethyl-2-[4-(4-pyrrolo[1,2-a]quinoxalin-4-ylpiperazin-1-
 yl)butyl]-3H-thieno[2,3-d]pyrimidin-4-one was obtained.

¹H-NMR(CDCl₃)δ:11.30(br s,1H),7.81(dd,J=1.2Hz,2.7Hz,1H),
 7.72(dd,J=1.5Hz,8.1Hz,1H),7.67~7.65(m,1H),7.34~7.24(m,2H),
 6.79~6.74(m,2H),3.90(t,J=4.8Hz,4H),2.76(t,J=7.2Hz,2H),
 2.67(t,J=4.8Hz,4H),2.51(t,J=6.9Hz,2H),2.48(s,3H),2.38(s,3H),
 1.94~1.86(m,2H),1.72~1.65(m,2H)
 Mass,m/e:486(M⁺),196(base)

Example 3-12

In the manner similar to Example 3-1,
5,6-dimethyl-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propyl]-3H-thieno-
[2,3-d]pyrimidin-4-one was obtained.

5 $^1\text{H-NMR}(\text{CDCl}_3)\delta$:12.92(br s,1H),7.99(d,J=9.3Hz,1H),
7.69(d,J=8.1Hz,1H),7.60(dd,J=1.5Hz,8.1Hz,1H),
7.53(ddd,J=1.5Hz,6.9Hz,8.5Hz,1H),7.25~7.21(m,1H),
6.99(d,J=9.3Hz,1H),4.02(t,J=5.0Hz,4H),2.89(t,J=6.2Hz,2H),
2.74(t,J=5.0Hz,4H),2.60~2.57(m,2H),2.45(s,3H),
10 2.37(d,J=0.8Hz,3H),2.01(t,J=6.2Hz,2H)
Mass,m/e:433(M^+),153(base)

Example 3-13

In the manner similar to Example 3-1,
15 7-ethoxycarbonyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-
3,4,5,6,7,8-hexahydro-4-oxa-9-thia-1,3,7-triaza-9H-fluorene was
obtained.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$:7.87(d,J=8.9Hz,1H),7.68(d,J=8.5Hz,1H),
20 7.58(dd,J=1.2Hz,8.1Hz,1H),
7.51(ddd,J=1.5Hz,6.9Hz,8.5Hz,1H),
7.21(ddd,J=1.2Hz,6.9Hz,8.1Hz,1H),6.96(d,J=9.2Hz,1H),
4.67(br s,2H),4.18(q,J=6.9Hz,2H),3.81(t,J=5.0Hz,4H),
3.76~3.72(m,2H),3.10(br s,2H),2.78(t,J=7.3Hz,2H),
25 2.60(t,J=5.0Hz,4H),2.47(t,J=6.9Hz,2H),1.98~1.86(m,2H),
1.70~1.63(m,4H)
Mass,m/e:546(M^+),157(base)

Example 3-14

30 In the manner similar to Example 3-1,
7-benzoyloxycarbonyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-
3,4,5,6,7,8-hexahydro-4-oxa-9-thia-1,3,7-triaza-9H-fluorene was
obtained.

35 $^1\text{H-NMR}(\text{CDCl}_3)\delta$:7.87(d,J=8.9Hz,1H),7.68(d,J=8.5Hz,1H),

7.58(d, J=8.1Hz, 1H), 7.53~7.49(m, 1H), 7.36~7.29(m, 5H),
 7.23~7.19(m, 1H), 6.96(d, J=9.2Hz, 1H), 5.17(s, 2H), 4.69(s, 2H),
 3.82(t, J=5.0Hz, 4H), 3.79~3.75(m, 2H), 3.11(br s, 2H),
 2.76(t, J=6.9Hz, 2H), 2.61(t, J=5.1Hz, 4H), 2.49~2.46(m, 2H),
 1.87(q, J=7.3Hz, 2H), 1.70~1.64(m, 4H)
 Mass, m/e: 395, 304(base), 91

Example 3-15

In a mixture of 5 ml of acetic acid with 2 ml of water 60 mg of
 3-amino-7-tert-butoxycarbonyl-2-[4-(4-quinolin-2-ylpiperazin-1-
 yl)butyl]-5,6,7,8-tetrahydro-3H-pyrido[4'3':4,5]thieno[2,3-d]pyrimidin-
 4-one was dissolved, and into the solution, a solution of 10 mg of
 sodium nitrite in 2 ml of water was dropped under cooling with ice.
 After 30 minutes' stirring, the reaction mixture was neutralized with
 saturated aqueous sodium hydrogencarbonate solution, and the
 resulting precipitate was extracted with chloroform, washed with
 water and dried over anhydrous sodium sulfate. Distilling the
 solvent off under reduced pressure, the residue was purified on silica
 gel column chromatography to provide 52 mg (99%) of
 7-acetyl-2-[4-(4-quinolin-2-
 ylpiperazin-1-yl)butyl]-5,6,7,8-tetrahydro-3H-pyrido[4'3':4,5]thieno-
 [2,3-d]pyrimidin-4-one.

¹H-NMR(CDCl₃) δ: 11.54(br s, 1H), 7.88(d, J=9.2Hz, 1H),
 7.68(d, J=8.5Hz, 1H), 7.58(dd, J=1.5Hz, 8.5Hz, 1H),
 7.52(ddd, J=1.5Hz, 6.9Hz, 8.5Hz, 1H),
 7.21(ddd, J=1.5Hz, 6.9Hz, 8.5Hz, 1H), 6.97(d, J=9.2Hz, 1H),
 4.79(br s, 2H), 3.83~3.81(m, 4H), 3.73(t, J=7.0Hz, 2H),
 3.17~3.12(m, 2H), 2.81~2.73(m, 2H), 2.65~2.60(m, 4H),
 2.49(t, J=6.4Hz, 2H), 2.19(s, 3H), 1.89(q, J=7.0Hz, 2H),
 1.67(q, J=7.0Hz, 2H)
 Mass, m/e: 516(M⁺), 372, 157(base)

Example 3-16

To 100 mg of 7-benzyloxycarbonyl-2-[4-(4-quinolin-2-

ylpiperazin-1-yl)butyl]-3,4,5,6,7,8-hexahydro-4-oxa-9-thia-1,3,7-triaza-9H-fluorene as synthesized in Example 3-14, 5 ml of hydrogen bromide-acetic acid solution was added and stirred at room temperature. After neutralizing the system with saturated aqueous sodium hydrogencarbonate solution, the reaction product was extracted with chloroform, dried over anhydrous magnesium sulfate and concentrated to provide 78 mg (100%) of 2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3,4,5,6,7,8-hexahydro-4-oxa-9-thia-1,3,7-triaza-9H-fluorene.

10

$^1\text{H-NMR}(\text{DMSO-}d_6)\delta$: 8.01(d, J=9.2Hz, 1H), 7.68(d, J=8.5Hz, 1H), 7.54~7.49(m, 2H), 7.35~7.32(m, 1H), 7.29~7.20(m, 1H), 4.03(br s, 2H), 3.77~3.66(m, 4H), 3.12~3.10(m, 2H), 2.93(br s, 2H), 2.67~2.64(m, 2H), 2.49~2.46(m, 4H), 2.36(t, J=7.0Hz, 2H), 1.76~1.70(m, 2H), 1.55~1.50(m, 2H)
Mass, m/e: 157(base), 128

15

Example 3-17

First, in the manner similar to Example 3-1, 7-benzyloxycarbonyl-2-[4-[4-(4-methylquinolin-2-yl)piperazin-1-yl]butyl]-3,4,5,6,7,8-hexahydro-4-oxa-9-thia-1,3,7-triaza-9H-fluorene was obtained. Then from this compound 2-[4-[4-(4-methylquinolin-2-yl)piperazin-1-yl]butyl]-3,4,5,6,7,8-hexahydro-4-oxa-9-thia-1,3,7-triaza-9H-fluorene trihydrobromide was prepared in the manner similar to Example 3-16.

20

25

$^1\text{H-NMR}(\text{DMSO-}d_6)\delta$: 12.47(s, 1H), 10.16(s, 1H), 9.20(s, 2H), 8.12(d, J=8.1Hz, 1H), 8.05(d, J=8.5Hz, 1H), 7.86~7.82(m, 1H), 7.63(br s, 1H), 7.60~7.56(m, 1H), 4.77~4.74(m, 2H), 4.62~4.21(m, 6H), 3.79~3.74(m, 4H), 3.16~3.13(m, 2H), 2.72(s, 3H), 2.59~2.49(m, 4H)
Mass, m/e: 488(M^+), 171(base)

30

Example 3-18

In the manner similar to Example 1-62,

35

7-acetyl-2-[4-[4-(4-methylquinolin-2-yl)piperazin-1-yl]butyl]-
 3,4,5,6,7,8-hexahydro-4-oxa-9-thia-1,3,7-triaza-9H-fluorene was
 obtained from 2-[4-[4-(4-methylquinolin-2-yl)piperazin-1-yl]butyl]-
 3,4,5,6,7,8-hexahydro-4-oxa-9-thia-1,3,7-triaza-9H-fluorene
 5 trihydrobromide as synthesized in Example 3-17.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.75(d, J=7.7Hz, 1H), 7.70(d, J=8.5Hz, 1H),
 7.54~7.50(m, 1H), 7.23~7.22(m, 2H), 6.83(s, 1H), 4.77(br s, 4H),
 3.78~3.72(m, 6H), 3.19(t, J=7.3Hz, 2H), 3.13~3.04(m, 2H),
 10 2.61~2.53(m, 6H), 2.59(s, 3H), 2.20(s, 3H), 1.98(q, J=6.9Hz, 2H)
 Mass, m/e: 225, 171(base), 142

Example 4: Syntheses of compounds of the formula (I) in which X¹
stands for amino, lower alkylamino, di-lower alkylamino or lower
 15 alkylideneamino, and Y is direct bond

Example 4-1

Step 4-1-A:

Into 7N-ammonia-methanol solution, 170 g of ethyl
 2-oxocyclohexanecarboxylate was added and stirred for an overnight
 20 at room temperature. Distilling the solvent off under reduced
 pressure, the resulting crude crystalline product was recrystallized
 from ethyl acetate-n-hexane to provide 152 g (90%) of ethyl
 2-aminocyclohex-1-enecarboxylate.

25 $^1\text{H-NMR}(\text{CDCl}_3)$: 4.14(q, J=7.3Hz, 2H), 2.25(d, J=5.9Hz, 2H),
 2.20(d, J=5.9Hz, 2H), 1.67~1.56(m, 4H)
 Mass, m/e: 169(M⁺), 96(base)

Step 4-1-B:

30 In 150 ml of tetrahydrofuran, 42.3 g of ethyl 2-aminocyclohex-
 1-enecarboxylate as synthesized in the above Step 4-1-A was
 dissolved, to which 40 g of pyridine was added, and into which
 5-bromovaleryl chloride was dropped under cooling with ice. After
 stirring the reaction mixture overnight at room temperature, ethyl
 35 acetate was added, followed by washing with saturated aqueous

sodium hydrogencarbonate solution, 10% aqueous citric acid and saturated brine, by the order stated. Drying the product over anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure. The residue was purified on silica gel column chromatography (n-hexane : ethyl acetate = 8:1), to provide 76.6 g (92%) of ethyl 2-(5-bromopentanoylamino)cyclohex-1-enecarboxylate.

¹H-NMR(CDCl₃): 11.62(br s, 1H), 4.22~4.09(m, 2H), 3.42(t, J=6.9Hz, 2H), 2.97~2.94(m, 2H), 2.34(t, J=7.0Hz, 2H), 2.32~2.23(m, 2H), 1.94~1.88(m, 2H), 1.85~1.79(m, 2H), 1.65~1.56(m, 4H), 1.30(t, J=7.0Hz, 3H)
Mass, m/e: 333(M⁺), 55(base)

Step 4-1-C:

In 350 ml of toluene, 66.5 g of ethyl 2-(5-bromopentanoylamino)cyclohex-1-enecarboxylate as synthesized in above Step 4-1-B, 46.9 g of 2-piperazin-1-ylquinoline and 22.3 g of triethylamine were dissolved and heated under reflux for an overnight. The solvent was distilled off under reduced pressure, and ethyl acetate was added to the residue, followed by washing with saturated aqueous sodium hydrogencarbonate solution. The organic layer was dried over anhydrous magnesium sulfate, and from which the solvent was distilled off under reduced pressure. Purifying the residue on silica gel column chromatography (n-hexane : ethyl acetate : methanol = 1:6:0.2) to provide 79.8 g (86%) of ethyl 2-[5-(4-quinolin-2-ylpiperazin-1-yl)pentanoylamino]cyclohex-1-enecarboxylate.

¹H-NMR(CDCl₃): 11.61(br s, 1H), 7.87(d, J=9.2Hz, 1H), 7.69(d, J=8.5Hz, 1H), 7.58~7.56(m, 1H), 7.51(ddd, J=1.5Hz, 6.9Hz, 8.5Hz, 1H), 7.20(ddd, J=1.2Hz, 6.9Hz, 8.1Hz, 1H), 6.97(d, J=9.2Hz, 1H), 4.16(q, J=6.9Hz, 2H), 3.74(t, J=5.0Hz, 4H), 2.97(t, J=5.0Hz, 2H), 2.56(t, J=5.0Hz, 4H), 2.43~2.90(m, 6H), 1.74~1.70(m, 2H), 1.68(m, 4H), 1.28(t, J=6.9Hz, 2H)

Mass, m/e: 464(M⁺), 157(base)

Step 4-1-D:

In 120 ml of ethanol, 8.0 g of ethyl 2-[5-(4-quinolin-2-ylpiperazin-1-yl)pentanoylamino]cyclohex-1-enecarboxylate as synthesized in above Step 4-1-C was dissolved, and to the solution 60 ml of hydrazine monohydrate was added, followed by 4 hours' heating under reflux. Distilling the solvent off under reduced pressure, the residue was dissolved in chloroform, washed with saturated aqueous sodium hydrogencarbonate solution and saturated brine, and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, the residue was purified on silica gel column chromatography (chloroform : methanol = 50:1) to provide 3.8 g (51%) of 3-amino-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-5,6,7,8-tetrahydro-3H-quinazolin-4-one.

¹H-NMR(CDCl₃)δ: 7.87(d, J=9.3Hz, 1H), 7.69(d, J=8.5Hz, 1H), 7.58(d, J=7.7Hz, 1H), 7.52(ddd, J=1.5Hz, 6.9Hz, 7.5Hz, 1H), 7.25~7.19(m, 1H), 6.97(d, J=8.9Hz, 1H), 4.93(s, 2H), 3.74(t, J=5.0Hz, 4H), 2.92(t, J=7.7Hz, 2H), 2.58~2.55(m, 6H), 2.52~2.49(m, 2H), 2.44(t, J=7.3Hz, 2H), 1.81~1.63(m, 8H)
Mass, m/e: 432(M⁺), 157(base)

Example 4-2

In the manner similar to Example 4-1, 3-amino-2-[4-[4-(4-methylquinolin-2-yl)piperazin-1-yl]butyl]-5,6,7,8-tetrahydro-3H-quinazolin-4-one was obtained.

¹H-NMR(CDCl₃)δ: 7.74(d, J=8.5Hz, 1H), 7.69(d, J=8.5Hz, 1H), 7.51(ddd, J=1.2Hz, 7.0Hz, 8.1Hz, 1H), 7.22(d, J=8.1Hz, 1H), 6.82(s, 1H), 4.94(s, 2H), 3.74(t, J=5.0Hz, 4H), 2.92(t, J=7.3Hz, 2H), 2.57(s, 3H), 2.56~2.54(m, 6H), 2.53~2.50(m, 2H), 2.44(t, J=7.3Hz, 2H), 1.82~1.62(m, 8H)
Mass, m/e: 446(M⁺), 171(base)

Example 4-3

In the manner similar to Example 4-1,
3-amino-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3H-quinazolin-4-one was obtained.

5

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.24(dd, $J=1.2\text{Hz}, 8.1\text{Hz}$, 1H),
7.88(d, $J=8.9\text{Hz}$, 1H), 7.73(ddd, $J=1.6\text{Hz}, 6.9\text{Hz}, 8.5\text{Hz}$, 1H),
7.71~7.65(m, 2H), 7.59(dd, $J=1.2\text{Hz}, 7.9\text{Hz}$, 1H),
7.52(ddd, $J=1.2\text{Hz}, 6.9\text{Hz}, 8.1\text{Hz}$, 1H),
10 7.44(ddd, $J=1.2\text{Hz}, 6.9\text{Hz}, 8.1\text{Hz}$, 1H),
7.21(ddd, $J=1.2\text{Hz}, 6.4\text{Hz}, 8.1\text{Hz}$, 1H), 6.97(d, $J=9.2\text{Hz}$, 1H),
4.91(s, 2H), 3.75(t, $J=4.8\text{Hz}$, 4H), 3.07(t, $J=7.7\text{Hz}$, 2H),
2.58(t, $J=5.0\text{Hz}$, 4H), 2.48(t, $J=7.3\text{Hz}$, 2H), 1.95~1.87(m, 2H),
1.76~1.69(m, 2H)
15 Mass, m/e : 428(M^+), 157(base)

Example 4-4

In the manner similar to Example 4-1,
3-amino-2-[4-[4-(4-methylquinolin-2-yl)piperazin-1-yl]butyl]-3H-
20 quinazolin-4-one was obtained.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.24(dd, $J=1.5\text{Hz}, 8.1\text{Hz}$, 1H),
7.77~7.65(m, 4H), 7.51(ddd, $J=1.5\text{Hz}, 6.9\text{Hz}, 8.5\text{Hz}$, 1H),
7.47~7.42(m, 1H), 7.23~7.21(m, 1H), 6.83(s, 1H), 4.91(s, 2H),
25 3.74(t, $J=5.0\text{Hz}$, 4H), 3.07(t, $J=7.3\text{Hz}$, 2H), 2.58(t, $J=5.4\text{Hz}$, 4H),
2.48(t, $J=7.3\text{Hz}$, 2H), 1.91(q, $J=7.7\text{Hz}$, 2H), 1.74(q, $J=7.7\text{Hz}$, 2H)
Mass, m/e : 428(M^+), 157(base)

Example 4-5

In the manner similar to Example 4-1,
3-amino-2-[4-[4-(3-methylquinolin-2-yl)piperazin-1-yl]butyl]-
5,6,7,8-tetrahydro-3H-quinazolin-4-one was obtained.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.83(d, $J=8.5\text{Hz}$, 1H), 7.77(s, 1H),
35 7.60(d, $J=8.1\text{Hz}$, 1H), 7.52(ddd, $J=1.5\text{Hz}, 6.9\text{Hz}, 8.5\text{Hz}$, 1H),

7.31(ddd, J=1.1Hz, 6.9Hz, 8.1Hz, 1H), 4.98(s, 2H),
 3.35~3.33(m, 4H), 2.93(t, J=7.3Hz, 2H), 2.64(br s, 4H),
 2.59(t, J=6.2Hz, 2H), 2.53~2.50(m, 2H), 2.47(t, J=7.3Hz, 2H),
 2.42(d, J=0.8Hz, 3H), 1.83~1.65(m, 8H)
 5 Mass, m/e: 446(M⁺), 171(base)

Example 4-6

In the manner similar to Example 4-1,
 3-amino-2-[4-[4-(3,4-dimethylquinolin-2-yl)piperazin-1-yl]butyl]-
 10 5,6,7,8-tetrahydro-3H-quinazolin-4-one was obtained.

¹H-NMR(CDCl₃)δ: 7.87(d, J=7.3Hz, 1H), 7.83(d, J=7.3Hz, 1H),
 7.53(t, J=8.1Hz, 1H), 7.37~7.35(m, 1H), 4.99(s, 2H), 3.27(br s, 4H),
 2.93(t, J=7.7Hz, 2H), 2.64(br s, 4H), 2.59(t, J=5.8Hz, 2H),
 15 2.55(s, 3H), 2.52(t, J=6.2Hz, 2H), 2.47~2.46(m, 2H), 2.37(s, 3H),
 1.81~1.67(m, 8H)
 Mass, m/e: 460(M⁺), 185(base)

Example 4-7

20 In the manner similar to Example 4-1,
 3-amino-2-[4-[4-(2,3-dihydro-1H-cyclopenta[c]quinolin-4-yl)-
 piperazin-1-yl]butyl]-5,6,7,8-tetrahydro-3H-quinazolin-4-one was
 obtained.

25 ¹H-NMR(CDCl₃)δ: 7.80(d, J=8.5Hz, 1H), 7.64(d, J=8.1Hz, 1H),
 7.53~7.49(m, 1H), 7.30~7.26(m, 1H), 4.96(s, 2H), 3.57(br s, 4H),
 3.17(t, J=7.3Hz, 2H), 3.04(t, J=7.3Hz, 2H), 2.93(t, J=7.7Hz, 2H),
 2.60~2.57(m, 6H), 2.52(t, J=6.2Hz, 2H), 2.47~2.44(m, 2H),
 2.22(q, J=7.3Hz, 2H), 1.82~1.65(m, 8H)
 30 Mass, m/e: 472(M⁺), 197(base)

Example 4-8

In the manner similar to Example 4-1,
 3-amino-2-[4-[4-(7,8,9,10-tetrahydrophenanthridin-6-yl)piperazin-
 35 1-yl]butyl]-5,6,7,8-tetrahydro-3H-quinazolin-4-one was obtained.

¹H-NMR(CDCl₃)δ:7.84~7.80(m,2H),7.53(t,J=8.1Hz,1H),
 7.37~7.33(m,1H),4.99(s,2H),3.31(br s,4H),3.10(t,J=6.6Hz,2H),
 2.95~2.91(m,2H),2.76(t,J=5.8Hz,2H),2.62(br s,4H),
 5 2.60~2.57(m,2H),2.52(t,J=6.2Hz,2H),2.49~2.45(m,2H),
 1.98~1.93(m,2H),1.82~1.65(m,10H)
 Mass,m/e:486(M⁺),211(base)

Example 4-9

10 In the manner similar to Example 4-1,
 3-amino-2-[4-[4-(3,4-dimethylquinolin-2-yl)piperazin-1-yl]butyl]-
 3H-quinazolin-4-one was obtained.

¹H-NMR(CDCl₃)δ:8.25~8.23(m,1H),7
 15 .87(dd,J=1.2Hz,8.5Hz,1H),7.85~7.82(m,1H),
 7.66(d,J=7.7Hz,1H),7.53(ddd,J=1.2Hz,6.9Hz,8.5Hz,1H),
 7.44(ddd,J=1.2Hz,6.9Hz,8.0Hz,1H),
 7.35(ddd,J=1.2Hz,6.9Hz,8.0Hz,1H),
 7.33(ddd,J=1.5Hz,6.9Hz,8.5Hz,1H),4.95(s,2H),3.28(br s,4H),
 20 3.10~3.06(m,2H),2.65(br s,4H),2.55(s,3H),2.53~2.49(m,2H),
 2.37(s,3H),1.95~1.88(m,2H),1.77~1.69(m,2H)
 Mass,m/e:456(M⁺),185(base)

Example 4-10

25 In the manner similar to Example 4-1,
 3-amino-2-[4-[4-(2,3-dihydro-1H-cyclopenta[c]quinolin-4-yl)-
 piperazin-1-yl]butyl]-3H-quinazolin-4-one was obtained.

¹H-NMR(CDCl₃)δ:8.24(dd,J=1.2Hz,8.1Hz,1H),
 30 7.80(d,J=8.1Hz,1H),7.73(ddd,J=1.5Hz,6.9Hz,8.5Hz,1H),
 7.67~7.63(m,2H),7.51(ddd,J=1.5Hz,6.9Hz,8.5Hz,1H),
 7.47~7.42(m,2H),7.28(ddd,J=1.2Hz,6.9Hz,8.1Hz,1H),
 4.93(s,2H),3.58(br s,4H),3.19~3.15(m,2H),3.10~3.03(m,4H),
 2.62(br s,4H),2.49(t,J=7.3Hz,2H),2.23(q,J=7.3Hz,2H),
 35 1.91(q,J=7.7Hz,2H),1.75~1.71(m,2H)

Mass, m/e: 468(M⁺), 197(base)

Example 4-11

In the manner similar to Example 4-1,

- 5 3-amino-2-[4-[4-(7,8,9,10-tetrahydrophenanthridin-6-yl)piperazin-1-yl]butyl]-3H-quinazolin-4-one was obtained.

¹H-NMR(CDCl₃)δ: 8.24(dd, J=1.5Hz, 8.5Hz, 1H),
 7.84~7.80(m, 2H), 7.73(ddd, J=1.5Hz, 6.9Hz, 8.5Hz, 1H),
 10 7.67(d, J=8.1Hz, 1H), 7.53(ddd, J=1.5Hz, 6.9Hz, 8.5Hz, 1H),
 7.44(ddd, J=1.2Hz, 6.9Hz, 8.1Hz, 1H),
 7.35(ddd, J=1.5Hz, 6.9Hz, 8.5Hz, 1H), 4.95(s, 2H),
 3.32(br s, 4H), 3.11~3.06(m, 4H), 2.76(t, J=5.8Hz, 2H),
 2.64(br s, 4H), 2.51(t, J=7.3Hz, 2H), 2.00~1.88(m, 2H),
 15 1.79~1.71(m, 2H)
 Mass, m/e: 482(M⁺), 211(base)

Example 4-12

In the manner similar to Example 4-1,

- 20 3-amino-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3H-pyrido[3,2-d]-pyrimidin-4-one was obtained.

¹H-NMR(CDCl₃)δ: 8.83(dd, J=1.5Hz, 4.2Hz, 1H),
 8.01(dd, J=1.5Hz, 8.5Hz, 1H), 7.88(d, J=9.2Hz, 1H),
 25 7.70~7.64(m, 2H), 7.58(d, J=2.1Hz, 1H), 7.54~7.50(m, 1H),
 7.23~7.19(m, 1H), 6.97(d, J=8.9Hz, 1H), 5.03(s, 2H),
 3.76(t, J=5.0Hz, 4H), 3.10(t, J=7.3Hz, 2H), 2.59(t, J=5.0Hz, 4H),
 2.48(t, J=7.3Hz, 2H), 1.92(q, J=7.7Hz, 2H), 1.76~1.71(m, 2H)
 Mass, m/e: 429(M⁺), 157(base)

30

Example 4-13

In the manner similar to Example 4-1,

- 3-amino-2-[4-(4-pyrrolo[1,2-a]quinoxalin-4-ylpiperazin-1-yl)butyl]-3H-quinazolin-4-one was obtained.

35

¹H-NMR(CDCl₃)δ:8.24(dd,J=1.2Hz,7.7Hz,1H),7.80(m,1H),
 7.75~7.73(m,1H),7.72(dd,J=1.5Hz,5.4Hz,1H),7.67~7.66(m,1H),
 7.65~7.64(m,1H),7.46~7.43(m,1H),7.33~7.28(m,1H),
 7.27~7.23(m,1H),6.77(dd,J=1.2Hz,3.9Hz,1H),
 5 6.75~6.73(m,1H),4.91(s,2H),3.82(t,J=5.0Hz,4H),
 3.08(t,J=7.7Hz,2H),2.65(t,J=5.0Hz,4H),2.50(t,J=7.3Hz,2H),
 1.91(q,J=7.7Hz,2H),1.77~1.69(m,2H)
 Mass,m/e:429(M⁺),157(base)

10 Example 4-14

In the manner similar to Example 4-1,
 3-amino-2-[4-(4-pyrrolo[1,2-a]quinoxalin-4-yl)piperazin-1-yl]butyl]-
 3H-pyrido[3,2-d]pyrimidin-4-one was obtained.

15 ¹H-NMR(CDCl₃)δ:8.84(dd,J=1.5Hz,4.2Hz,1H),
 8.00(dd,J=1.5Hz,6.1Hz,1H),7.80(dd,J=1.5Hz,2.7Hz,1H),
 7.71(dd,J=1.5Hz,8.1Hz,1H),7.66(dd,J=1.5Hz,3.1Hz,1H),
 7.65~7.64(m,1H),7.33~7.22(m,2H),6.77~6.73(m,2H),5.04(s,2H),
 3.82(t,J=5.0Hz,4H),3.10(t,J=7.7Hz,2H),2.65(t,J=5.0Hz,4H),
 20 2.51(t,J=7.3Hz,2H),1.92(q,J=7.3Hz,2H),1.73(q,J=7.3Hz,2H)
 Mass,m/e:468(M⁺),196(base)

Example 4-15

In the manner similar to Example 4-1,
 25 3-amino-7-chloro-2-[4-(4-quinolin-2-yl)piperazin-1-yl]butyl]-3H-
 quinazolin-4-one was obtained.

30 ¹H-NMR(CDCl₃)δ:8.16(d,J=8.5Hz,1H),7.88(d,J=8.9Hz,1H),
 7.69(d,J=8.5Hz,1H),7.67(d,J=1.9Hz,1H),7.58(d,J=8.1Hz,1H),
 7.52(ddd,J=1.5Hz,6.9Hz,8.1Hz,1H),7.43(d,J=1.9Hz,1H),
 7.38(d,J=2.3Hz,1H),7.21(ddd,J=1.2Hz,6.9Hz,8.1Hz,1H),
 6.97(d,J=9.2Hz,1H),4.89(s,2H),3.76(t,J=5.0Hz,4H),
 3.06(t,J=7.3Hz,2H),2.58(t,J=5.0Hz,4H),2.48(t,J=7.3Hz,2H),
 1.90(q,J=7.7Hz,2H),1.71(q,J=7.3Hz,2H)
 35 Mass,m/e:462(M⁺),157(base)

Example 4-16

In the manner similar to Example 4-1,
3-amino-6-bromo-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3H-
5 quinazolin-4-one was obtained.

¹H-NMR(CDCl₃)δ:8.37(d,J=2.3Hz,1H),7.88(d,J=9.3Hz,1H),
7.80(dd,J=2.3Hz,8.9Hz,1H),7.79(d,J=8.5Hz,1H),
7.58(d,J=7.7Hz,1H),7.54~7.50(m,2H),7.23~7.19(m,1H),
10 6.97(d,J=9.2Hz,1H),4.91(s,2H),3.75(t,J=5.0Hz,4H),
3.06(t,J=7.7Hz,2H),2.58(t,J=5.0Hz,4H),2.48(t,J=7.3Hz,2H),
1.90(t,J=7.3Hz,2H),1.71(t,J=7.7Hz,2H)
Mass,m/e:506(M⁺),157(base)

15 Example 4-17

In the manner similar to Example 4-1,
3-amino-6,7,8-trimethoxy-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-
3H-quinazolin-4-one was obtained.

20 ¹H-NMR(CDCl₃)δ:7.87(d,J=9.2Hz,1H),7.69(d,J=8.5Hz,1H),
7.58(dd,J=1.2Hz,8.5Hz,1H),
7.58(ddd,J=1.5Hz,7.0Hz,8.5Hz,1H),
7.38(s,1H),7.21(ddd,J=1.2Hz,6.9Hz,8.1Hz,1H),
6.97(d,J=9.2Hz,1H),4.91(s,2H),4.08(s,3H),4.02(s,3H),
25 3.96(s,3H),3.75(t,J=5.0Hz,4H),3.07(t,J=7.7Hz,2H),
2.58(t,J=5.0Hz,4H),2.47(t,J=7.7Hz,2H),1.92(q,J=7.7Hz,2H),
1.72(q,J=7.7Hz,2H)
Mass,m/e:157(base)

30 Example 4-18

In the manner similar to Example 4-1,
3-amino-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3H-thieno[3,2-d]-
pyrimidin-4-one was obtained.

35 ¹H-NMR(CDCl₃)δ:7.88(d,J=9.2Hz,1H),7.76(d,J=5.0Hz,1H),

7.69(d, J=7.3Hz, 1H), 7.58(dd, J=1.5Hz, 8.0Hz, 1H),
 7.52(ddd, J=1.5Hz, 6.9Hz, 8.1Hz, 1H), 7.27(d, J=5.4Hz, 1H),
 7.21(ddd, J=1.2Hz, 6.9Hz, 8.1Hz, 1H), 6.97(d, J=9.2Hz, 1H),
 4.94(s, 2H), 3.75(t, J=5.0Hz, 4H), 3.08(t, J=7.7Hz, 2H),
 5 2.58(t, J=5.0Hz, 4H), 2.47(t, J=7.7Hz, 2H), 1.89(q, J=7.7Hz, 2H),
 1.71(q, J=7.7Hz, 2H)
 Mass, m/e: 434(M⁺), 157(base)

Example 4-19

10 In the manner similar to Example 4-1,
 3-amino-8-methyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3H-
 quinazolin-4-one was obtained.

¹H-NMR(CDCl₃) δ: 8.08(dd, J=0.8Hz, 8.1Hz, 1H),
 15 7.88(d, J=8.9Hz, 1H), 7.69(d, J=8.5Hz, 1H),
 7.58(ddd, J=1.5Hz, 6.2Hz, 7.7Hz, 1H),
 7.52(ddd, J=1.5Hz, 6.9Hz, 8.5Hz, 1H), 7.32(t, J=7.7Hz, 1H),
 7.23~7.19(m, 1H), 6.97(d, J=9.2Hz, 1H), 4.88(s, 2H),
 3.76(t, J=5.0Hz, 4H), 3.07(t, J=7.7Hz, 2H), 2.59(t, J=5.4Hz, 4H),
 20 2.50(t, J=7.7Hz, 2H), 1.95(q, J=7.3Hz, 2H), 1.77~1.73(m, 2H)
 Mass, m/e: 442(M⁺), 157(base)

Example 4-20

25 In the manner similar to Example 4-1,
 3-amino-6-methyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3H-
 quinazolin-4-one was obtained.

¹H-NMR(CDCl₃) δ: 8.02(s, 1H), 7.88(d, J=8.9Hz, 1H),
 7.69(d, J=8.5Hz, 1H), 7.59~7.50(m, 4H), 7.23~7.19(m, 1H),
 30 6.97(d, J=9.2Hz, 1H), 4.90(s, 2H), 3.75(t, J=5.0Hz, 4H),
 3.06(t, J=1.7Hz, 2H), 2.58(t, J=5.0Hz, 4H), 2.49~2.44(m, 2H),
 2.48(s, 3H), 1.90(q, J=7.7Hz, 2H), 1.72(q, J=7.7Hz, 2H)
 Mass, m/e: 442(M⁺), 157(base)

35 Example 4-21

In the manner similar to Example 4-1,
3-amino-5-methyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3H-quinazolin-4-one was obtained.

5 $^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.08(d, J=8.1Hz, 1H), 7.88(d, J=9.2Hz, 1H),
7.69(d, J=8.1Hz, 1H), 7.59~7.54(m, 2H), 7.54~7.50(m, 1H),
7.32(t, J=7.7Hz, 1H), 7.23~7.20(m, 1H), 6.97(d, J=9.2Hz, 1H),
4.89(s, 2H), 3.75(t, J=5.0Hz, 4H), 3.07(t, J=7.3Hz, 2H), 2.61(s, 3H),
2.58(t, J=5.0Hz, 4H), 2.49(t, J=7.7Hz, 2H), 1.93(q, J=7.7Hz, 2H),
10 1.77~1.70(m, 2H)
Mass, m/e: 442(M^+), 157(base)

Example 4-22

In the manner similar to Example 4-1,
15 3-amino-2-[4-(4-methoxyquinolin-2-yl)piperazin-1-yl]butyl-3H-quinazolin-4-one was obtained.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.28(d, J=10.0Hz, 1H), 8.25~8.23(m, 1H),
7.66(d, J=8.1Hz, 1H), 7.47~7.40(m, 2H),
20 7.32(ddd, J=1.5Hz, 6.9Hz, 8.5Hz, 1H), 7.29(d, J=8.5Hz, 1H),
6.91(d, J=9.2Hz, 1H), 6.56(d, J=6.9Hz, 1H), 4.91(s, 2H), 3.94(s, 3H),
3.75(t, J=5.0Hz, 4H), 3.07(t, J=7.7Hz, 2H), 2.58(t, J=5.1Hz, 4H),
2.48(t, J=7.7Hz, 2H), 1.91(q, J=7.7Hz, 2H), 1.76~1.69(m, 2H)
Mass, m/e: 458(M^+), 187(base)

25

Example 4-23

In the manner similar to Example 4-1,
3-amino-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3H-thieno[2,3-d]-pyrimidin-4-one was obtained.

30

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.88(d, J=9.2Hz, 1H), 7.79(d, J=8.4Hz, 1H),
7.58(d, J=8.1Hz, 1H), 7.52(m, 1H), 7.42(d, J=5.8, 1H),
7.23~7.18(m, 2H), 6.97(d, J=9.2Hz, 1H), 6.56(d, J=6.9Hz, 1H),
4.93(s, 2H), 3.75(t, J=5.0Hz, 4H), 3.07(t, J=7.7Hz, 2H),
35 2.58(t, J=5.0Hz, 4H), 2.48(t, J=7.7Hz, 2H), 1.89~1.87(m, 2H),

1.72~1.70(m,2H)

Mass,m/e:434(M⁺),157(base)

Example 4-24

- 5 In the manner similar to Example 4-1,
3-amino-8-chloro-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3H-
quinazolin-4-one was obtained.

- ¹H-NMR(CDCl₃)δ:8.16(dd,J=1.5Hz,8.1Hz,1H),
10 7.88(d,J=9.2Hz,1H),7.81(dd,J=1.5Hz,8.1Hz,1H),
7.69(d,J=8.5Hz,1H),7.58(d,J=7.7Hz,1H),
7.52(ddd,J=1.5Hz,6.9Hz,8.5Hz,1H),7.38~7.34(m,1H),
7.23~7.19(m,1H),6.97(d,J=9.2Hz,1H),4.93(s,2H),
3.76(t,J=5.0Hz,4H),3.12(t,J=7.7Hz,2H),2.60(t,J=5.0Hz,4H),
15 2.50(t,J=7.7Hz,2H),1.95(q,J=7.7Hz,2H),1.75(q,J=7.7Hz,2H)
Mass,m/e:462(M⁺),157(base)

Example 4-25

- In the manner similar to Example 4-1,
20 3-amino-5-chloro-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3H-
quinazolin-4-one was obtained.

- ¹H-NMR(CDCl₃)δ:7.88(d,J=9.2Hz,1H),7.69(d,J=8.5Hz,1H),
7.59~7.50(m,4H),7.44(dd,J=2.7Hz,6.6Hz,1H),7.23~7.19(m,1H),
25 6.97(d,J=8.9Hz,1H),4.86(s,2H),3.76(t,J=5.0Hz,4H),
3.05(t,J=7.7Hz,2H),2.59(t,J=5.0Hz,4H),2.48(t,J=7.7Hz,2H),
1.89(q,J=7.7Hz,2H),1.75~1.69(m,2H)
Mass,m/e:462(M⁺),157(base)

Example 4-26

- In the manner similar to Example 4-1,
3-amino-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3H-benzo-
[g]quinazolin-4-one was obtained.

- 35 ¹H-NMR(CDCl₃)δ:8.87(s,1H),8.17(s,1H),8.05(d,J=7.7Hz,1H),

7.97(d, J=8.1Hz, 1H), 7.88(d, J=8.3Hz, 1H), 7.69(d, J=8.5Hz, 1H),
 7.62~7.58(m, 2H), 7.55~7.51(m, 2H), 7.24~7.20(m, 1H),
 6.98(d, J=9.2Hz, 1H), 4.87(s, 2H), 3.77(t, J=5.0Hz, 4H),
 3.11(t, J=7.7Hz, 2H), 2.60(t, J=5.0Hz, 4H), 2.51(t, J=7.7Hz, 2H),
 1.96(q, J=7.7Hz, 2H), 1.76(q, J=7.7Hz, 2H)
 Mass, m/e: 478(M⁺), 157(base)

Example 4-27

In the manner similar to Example 4-1,
 3-amino-8-fluoro-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3H-
 quinazolin-4-one was obtained.

¹H-NMR(CDCl₃)δ: 7.88(d, J=9.2Hz, 1H), 7.69(d, J=8.9Hz, 1H),
 7.66~7.62(m, 1H), 7.59(d, J=8.1Hz, 1H), 7.54~7.51(m, 1H),
 7.45(d, J=8.5Hz, 1H), 7.23~7.19(m, 1H), 7.11~7.06(m, 1H),
 6.97(d, J=8.9Hz, 1H), 4.86(s, 2H), 3.76(br s, 4H),
 3.06(t, J=7.7Hz, 2H), 2.59(br s, 4H), 2.50~2.46(m, 2H),
 1.92~1.87(m, 2H), 1.72~1.70(m, 2H)
 Mass, m/e: 446(M⁺), 157(base)

Example 4-28

In the manner similar to Example 4-1,
 3-amino-5-hydrazino-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3H-
 quinazolin-4-one was obtained.

¹H-NMR(CDCl₃)δ: 9.15(s, 2H), 7.88(d, J=9.2Hz, 1H),
 7.69(d, J=8.5Hz, 1H), 7.58(d, J=8.5Hz, 1H), 7.55~7.50(m, 2H),
 7.23~7.19(m, 1H), 7.00(d, J=7.3Hz, 1H), 6.97(d, J=8.9Hz, 1H),
 6.87~6.85(m, 1H), 4.73(s, 2H), 3.76~3.74(m, 4H), 3.63(s, 2H),
 3.00(t, J=7.7Hz, 2H), 2.58(t, J=5.0Hz, 4H), 2.47(t, J=7.3Hz, 2H),
 1.87(q, 2H), 1.72~1.68(m, 2H)
 Mass, m/e: 446(M⁺), 157(base)

Example 4-29

In the manner similar to Example 4-1,

3-amino-7-methyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3H-quinazolin-4-one was obtained.

¹H-NMR(CDCl₃)δ: 8.11(d, J=8.5Hz, 1H), 7.88(d, J=9.2Hz, 1H),
 5 7.69(d, J=8.1Hz, 1H), 7.58(d, J=7.0Hz, 1H),
 7.52(ddd, J=1.5Hz, 6.9Hz, 8.5Hz, 1H), 7.27(m, 1H),
 7.23~7.19(m, 2H), 6.97(d, J=9.2Hz, 1H), 4.88(s, 2H),
 3.76(t, J=5.0Hz, 4H), 3.07~3.04(m, 2H), 2.61(s, 3H),
 2.58(t, J=5.0Hz, 4H), 2.49~2.46(m, 2H), 2.48(s, 3H),
 10 1.90(q, J=7.7Hz, 2H), 1.72(q, J=7.7Hz, 2H)
 Mass, m/e: 442(M⁺), 157(base)

Example 4-30

In the manner similar to Example 4-1,
 15 3-amino-5-methyl-4-oxo-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-
 3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxylic acid ethyl ester was
 obtained.

¹H-NMR(CDCl₃)δ: 7.88(d, J=8.9Hz, 1H), 7.69(d, J=8.5Hz, 1H),
 20 7.58(d, J=8.1Hz, 1H), 7.54~7.52(m, 1H), 7.23~7.21(m, 1H),
 6.97(d, J=9.2Hz, 1H), 4.88(s, 2H), 3.75(t, J=5.0Hz, 4H),
 3.06(t, J=5.0Hz, 2H), 2.93(s, 3H), 2.58(t, J=5.0Hz, 4H),
 2.48~2.45(m, 2H), 1.88~1.86(m, 2H), 1.71~1.69(m, 2H),
 1.39(t, J=6.9Hz, 3H)
 25 Mass, m/e: 520(M⁺), 157(base)

Example 4-31

In the manner similar to Example 4-1,
 3-amino-2-[4-[4-(5-methoxyquinolin-2-yl)piperazin-1-yl]butyl]-
 30 5,6,7,8-tetrahydro-3H-quinazolin-4-one was obtained.

¹H-NMR(CDCl₃)δ: 8.28(d, J=9.6Hz, 1H), 7.44~7.40(m, 1H),
 7.28(d, J=7.7Hz, 1H), 6.92(d, J=9.2Hz, 1H), 6.58(d, J=7.3Hz, 1H),
 4.94(s, 2H), 3.98(s, 3H), 3.75(t, J=5.0Hz, 4H), 2.94~2.90(s, 3H),
 35 2.60~2.55(m, 6H), 2.44(t, J=7.7Hz, 2H), 1.83~1.60(m, 8H)

Mass, m/e: 462(M⁺), 187(base)

Example 4-32

In the manner similar to Example 4-1,

- 5 3-amino-6-phenyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-
5,6,7,8-tetrahydro-3H-quinazolin-4-one was obtained.

¹H-NMR(CDCl₃) δ: 7.88(d, J=8.8Hz, 1H), 7.79(d, J=8.4Hz, 1H),
7.58(d, J=8.1Hz, 1H), 7.52(ddd, J=1.2Hz, 6.9Hz, 8.1Hz, 1H),
10 7.34~7.19(m, 6H), 6.98(d, J=9.2Hz, 1H), 4.96(s, 2H),
3.76(t, J=5.0Hz, 4H), 2.95(t, J=7.7Hz, 2H), 2.75(m, 2H),
2.58(t, J=5.0Hz, 4H), 2.46(t, J=7.3Hz, 2H), 2.16~2.12(m, 1H),
1.96~1.61(m, 8H)
Mass, m/e: 508(M⁺), 157(base)

15

Example 4-33

In the manner similar to Example 4-1,

- 3-amino-2-[4-[4-(4,8-dimethylquinolin-2-yl)piperazin-1-yl]butyl]-
5,6,7,8-tetrahydro-3H-quinazolin-4-one was obtained.

20

¹H-NMR(CDCl₃) δ: 7.63(d, J=8.1Hz, 1H), 7.40(d, J=6.9Hz, 1H),
7.15~7.12(m, 1H), 6.82(s, 1H), 4.95(s, 2H), 3.75(t, J=5.0Hz, 4H),
2.93(t, J=7.7Hz, 2H), 2.64(s, 3H), 2.60~2.56(m, 6H), 2.58(s, 3H),
2.53~2.50(m, 2H), 2.44(t, J=7.3Hz, 2H), 1.84~1.61(m, 8H)
25 Mass, m/e: 460(M⁺), 185(base)

Example 4-34

In the manner similar to Example 4-1,

- 3-amino-2-[4-[4-(4,8-dimethylquinolin-2-yl)piperazin-1-yl]butyl]-
30 3H-quinazolin-4-one was obtained.

¹H-NMR(CDCl₃) δ: 8.24(dd, J=1.2Hz, 8.1Hz, 1H),
7.76~7.71(m, 1H), 7.66(d, J=7.7Hz, 1H), 7.62(d, J=7.7Hz, 1H),
7.47~7.43(m, 1H), 7.40(d, J=6.9Hz, 1H), 7.15~7.12(m, 1H),
35 6.82(s, 1H), 4.92(s, 2H), 3.75(t, J=5.0Hz, 4H), 3.08(t, J=7.7Hz, 2H),

2.64(s,3H),2.60~2.58(m,4H),2.58(s,3H),2.48(t,J=7.7Hz,2H),
 1.93~1.87(m,2H),1.75~1.71(m,2H)
 Mass,m/e:456(M⁺),185(base)

5 Example 4-35

In the manner similar to Example 4-1,
 3-amino-5,6-dimethyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3H-
 thieno[2,3-d]pyrimidin-4-one was obtained.

10 ¹H-NMR(CDCl₃)δ:7.88(d,J=9.2Hz,1H),7.79(d,J=8.1Hz,1H),
 7.58(dd,J=1.2Hz,8.1Hz,1H),
 7.52(ddd,J=1.5Hz,6.9Hz,8.5Hz,1H),7.23~7.19(m,1H),
 6.97(d,J=9.2Hz,1H),4.88(s,2H),3.76(t,J=5.0Hz,4H),
 3.04(t,J=7.7Hz,2H),2.57(t,J=5.0Hz,4H),2.46~2.44(m,2H),
 15 2.46(d,J=0.8Hz,3H),2.37(d,J=0.8Hz,3H),1.88~1.82(m,2H),
 1.72~1.66(m,2H)
 Mass,m/e:462(M⁺),157(base)

Example 4-36

20 In the manner similar to Example 4-1,
 3-amino-8-methyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-5,6,7,8-
 tetrahydro-3H-quinazolin-4-one was obtained.

¹H-NMR(CDCl₃)δ:7.88(d,J=8.9Hz,1H),7.69(d,J=7.7Hz,1H),
 25 7.58(d,J=8.1Hz,1H),7.54~7.50(m,1H),7.23~7.19(m,1H),
 6.97(d,J=9.0Hz,1H),4.92(s,2H),3.75(t,J=5.0Hz,4H),
 2.92(t,J=7.7Hz,2H),2.66~2.65(m,1H),2.57(t,J=5.0Hz,4H),
 2.56~2.40(m,4H),1.87~1.57(m,11H)
 Mass,m/e:446(M⁺),157(base)

30

Example 4-37

In the manner similar to Example 4-1,
 3-amino-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-5,5a,6,7,8,9,9a,10-
 octahydro-3H-benzo[g]quinazolin-4-one was obtained.

35

¹H-NMR(CDCl₃)δ:7.88(d,J=8.9Hz,1H),7.69(d,J=8.9Hz,1H),
 7.58(d,J=8.1Hz,1H),7.52(ddd,J=1.5Hz,6.9Hz,8.5Hz,1H),
 7.23~7.19(m,1H),6.97(d,J=9.2Hz,1H),4.93(s,2H),
 3.75(t,J=5.0Hz,4H),2.95~2.90(m,2H),2.64~2.57(m,8H),
 2.45(t,J=7.7Hz,2H),2.04~1.98(m,2H),1.83~1.40(m,14H)
 Mass,m/e:486(M⁺),157(base)

Example 4-38

In the manner similar to Example 4-1,
 3-amino-5,7-dimethyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-
 5,6,7,8-tetrahydro-3H-quinazolin-4-one was obtained.

¹H-NMR(CDCl₃)δ:7.88(d,J=9.2Hz,1H),7.69(d,J=8.1Hz,1H),
 7.58(d,J=7.7Hz,1H),7.54~7.50(m,1H),7.23~7.19(m,1H),
 6.97(d,J=9.2Hz,1H),4.93(s,2H),3.75(t,J=5.0Hz,4H),
 2.91(t,J=7.7Hz,2H),2.57(m,6H),2.44(t,J=7.7Hz,2H),
 2.27~2.22(m,1H),2.03~1.98(m,1H),1.84~1.63(m,6H),
 1.30(d,J=6.6Hz,3H),1.03(d,J=6.6Hz,3H)
 Mass,m/e:460(M⁺),157(base)

Example 4-39

In the manner similar to Example 4-1,
 3-amino-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-5,6,7-trihydro-
 3H-cyclopenta[d]pyrimidin-4-one was obtained.

¹H-NMR(CDCl₃)δ:7.88(d,J=9.3Hz,1H),7.69(d,J=8.5Hz,1H),
 7.58(d,J=7.7Hz,1H),7.52(ddd,J=1.5Hz,6.9Hz,8.5Hz,1H),
 7.21(ddd,J=1.2Hz,7.0Hz,8.1Hz,1H),6.97(d,J=9.2Hz,1H),
 4.97(s,2H),3.75(t,J=5.0Hz,4H),2.97(t,J=7.7Hz,2H),
 2.86~2.80(m,4H),2.57(t,J=5.0Hz,4H),2.45(t,J=7.5Hz,2H),
 2.08(t,J=7.7Hz,2H),1.84~1.78(m,2H),1.70~1.61(m,2H)
 Mass,m/e:418(M⁺),402,157(base)

Example 4-40

In the manner similar to Example 4-1,

3-amino-8-methoxy-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3H-quinazolin-4-one was obtained.

¹H-NMR(CDCl₃)δ: 7.87(d, J=9.2Hz, 1H),
 5 7.81(dd, J=0.8Hz, 8.1Hz, 1H), 7.69(d, J=8.4Hz, 1H),
 7.58(d, J=8.1Hz, 1H), 7.52(ddd, J=1.5Hz, 6.9Hz, 8.5Hz, 1H),
 7.39~7.36(m, 1H), 7.22~7.20(m, 1H), 7.17(d, J=6.9Hz, 1H),
 6.97(d, J=9.2Hz, 1H), 4.96(s, 2H), 4.00(s, 3H), 3.75(t, J=4.6Hz, 4H),
 3.12(t, J=8.1Hz, 2H), 2.58(t, J=5.0Hz, 4H), 2.47(t, J=7.3Hz, 2H),
 10 1.94~1.86(m, 2H), 1.75~1.68(m, 2H)
 Mass, m/e: 458(M⁺), 442, 157(base)

Example 4-41

In the manner similar to Example 4-1,
 15 3-amino-6,7-dimethoxy-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3H-quinazolin-4-one was obtained.

¹H-NMR(CDCl₃)δ: 7.88(d, J=9.3Hz, 1H), 7.69(d, J=8.1Hz, 1H),
 7.59(d, J=8.1Hz, 1H), 7.53(s, 1H),
 20 7.52(ddd, J=1.5Hz, 6.9Hz, 8.5Hz, 1H),
 7.22(ddd, J=1.2Hz, 6.9Hz, 8.1Hz, 1H), 7.06(s, 1H),
 6.97(d, J=9.2Hz, 1H), 4.90(s, 2H), 3.99(br s, 6H), 3.75(m, 4H),
 3.05(t, J=7.7Hz, 2H), 2.63(m, 4H), 2.51(t, J=6.9Hz, 2H),
 1.92~1.86(m, 2H), 1.78~1.71(m, 2H)
 25 Mass, m/e: 488(M⁺), 472, 157(base)

Example 4-42

In the manner similar to Example 4-1,
 3-amino-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-5,6,7,8,9-
 30 pentahydro-3H-cyclohepta[d]pyrimidin-4-one was obtained.

¹H-NMR(CDCl₃)δ: 7.88(d, J=9.3Hz, 1H), 7.69(d, J=8.1Hz, 1H),
 7.58(d, J=9.1Hz, 1H), 7.52(ddd, J=1.2Hz, 6.9Hz, 8.1Hz, 1H),
 7.22~7.20(m, 1H), 6.97(d, J=9.3Hz, 1H), 5.00(s, 2H),
 35 3.75(t, J=5.0Hz, 4H), 2.91(t, J=7.3Hz, 2H), 2.75(t, J=8.5Hz, 2H),

2.58(t, J=5.0Hz, 4H), 2.45(t, J=7.3Hz, 2H), 1.83~1.78(m, 4H),
 1.70~1.60(m, 6H)
 Mass, m/e: 446(M⁺), 430, 157(base)

5 Example 4-43

In the manner similar to Example 4-1, 4-amino-12-methyl-5-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-4,6,12-triaza-tricyclo-[7.2.1.0^{2,7}]dodeca-2(7),5-dien-3-one was obtained.

10 ¹H-NMR(CDCl₃)δ: 7.87(d, J=9.2Hz, 1H), 7.69(d, J=7.5Hz, 1H),
 7.58(d, J=8.1Hz, 1H), 7.53~7.50(m, 1H), 7.23~7.21(m, 1H),
 6.95(d, J=9.2Hz, 1H), 5.00(s, 2H), 3.74(t, J=5.0Hz, 4H), 3.11(s, 3H),
 2.87(t, J=5.3Hz, 4H), 2.56~2.53(m, 4H), 2.45~2.37(m, 4H),
 2.06~1.54(m, 8H)
 15 Mass, m/e: 281, 255, 171, 157(base), 145, 128

Example 4-44

Step 4-44-A: In the manner similar to Example 4-1,

3-amino-6-tert-butoxycarbonyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)-
 20 butyl]-5,6,7,8-tetrahydro-3H-pyrido[4,3-d]pyrimidin-4-one was
 obtained.

¹H-NMR(CDCl₃)δ: 7.88(d, J=9.3Hz, 1H), 7.69(d, J=8.1Hz, 1H),
 7.58(d, J=8.1Hz, 1H), 7.52(ddd, J=1.5Hz, 6.9Hz, 8.5Hz, 1H),
 25 7.21(ddd, J=1.2Hz, 7.0Hz, 8.1Hz, 1H), 6.97(d, J=8.8Hz, 1H),
 4.96(s, 2H), 4.35(s, 2H), 3.75(t, J=5.0Hz, 4H), 3.65(t, J=5.7Hz, 2H),
 2.95(t, J=7.7Hz, 2H), 2.57(t, J=5.0Hz, 4H), 2.45(t, J=7.4Hz, 2H),
 1.84~1.77(m, 2H), 1.70~1.64(m, 2H), 1.48(s, 9H)
 Mass, m/e: 533(M⁺), 433, 157(base)

30

Step 4-44-B:

To 10 ml of 4N-hydrochloric acid-dioxane solution, 53 mg of
 3-amino-6-tert-butoxycarbonyl-2-[4-(4-quinolin-2-ylpiperazin-1-
 yl)butyl]-5,6,7,8-tetrahydro-3H-pyrido[4,3-d]pyrimidin-4-one as
 35 synthesized in above Step 4-44-A was added and stirred for 18 hours

at room temperature. The solution was neutralized with saturated aqueous sodium hydrogencarbonate solution, extracted with ethyl acetate, dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified
 5 on silica gel column chromatography (chloroform : methanol =9:1) to provide 39 mg (90%) of
 3-amino-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-5,6,7,8-tetrahydro-3H-pyrido[4,3-d]pyrimidin-4-one.

10 $^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.88(d, J=8.7Hz, 1H), 7.69(d, J=8.1Hz, 1H), 7.58(d, J=8.1Hz, 1H), 7.52(ddd, J=1.5Hz, 6.9Hz, 8.5Hz, 1H), 7.23~7.17(m, 1H), 6.97(d, J=9.3Hz, 1H), 4.95(s, 2H), 3.80(s, 2H), 3.75(t, J=4.6Hz, 4H), 3.10(t, J=5.8Hz, 2H), 2.95(t, J=7.7Hz, 2H), 2.62(t, J=5.8Hz, 2H), 2.58(t, J=5.2Hz, 4H), 2.45(t, J=7.4Hz, 2H),
 15 2.35(s, 1H), 1.83~1.79(m, 2H), 1.69~1.64(m, 2H)
 Mass, m/e: 433(M^+ , base), 417, 157

Example 4-45

In the manner similar to Example 4-1,
 20 3-amino-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propyl]-5,6,7,8-tetrahydro-3H-quinazolin-4-one was obtained.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.88(d, J=9.2Hz, 1H), 7.69(d, J=8.1Hz, 1H), 7.58(d, J=7.7Hz, 1H), 7.54~7.50(m, 1H), 7.24~7.20(m, 1H),
 25 6.95(d, J=9.2Hz, 1H), 5.57(s, 2H), 3.70(t, J=5.0Hz, 4H), 3.01~2.98(m, 2H), 2.61~2.50(m, 8H), 2.47~2.44(m, 2H), 2.05(q, J=6.9Hz, 2H), 1.82~1.70(m, 4H)
 Mass, m/e: 418(M^+), 157(base)

Example 4-46

In the manner similar to Example 4-1,
 3-amino-2-[2-(4-quinolin-2-ylpiperazin-1-yl)ethyl]-5,6,7,8-tetrahydro-3H-quinazolin-4-one was obtained.

35 $^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.89(d, J=9.2Hz, 1H), 7.69(d, J=8.5Hz, 1H),

7.69(d, J=8.9Hz, 1H), 7.52(ddd, J=1.5Hz, 6.9Hz, 8.5Hz, 1H),
 7.24~7.20(m, 1H), 6.96(d, J=9.2Hz, 1H), 5.71(s, 2H),
 3.72(t, J=5.0Hz, 4H), 3.14(t, J=6.5Hz, 2H), 2.86(t, J=6.5Hz, 2H),
 2.69(t, J=5.0Hz, 4H), 2.59(t, J=6.2Hz, 2H), 2.53(t, J=6.2Hz, 2H),
 1.81~1.72(m, 4H)
 Mass, m/e: 404(M⁺), 157(base)

Example 4-47

In the manner similar to Example 4-1,
 3-amino-2-[5-(4-quinolin-2-ylpiperazin-1-yl)pentyl]-5,6,7,8-
 tetrahydro-3H-quinazolin-4-one was obtained.

¹H-NMR(CDCl₃)δ: 7.87(d, J=8.9Hz, 1H), 7.69(d, J=8.5Hz, 1H),
 7.58(d, J=8.2Hz, 1H), 7.54~7.50(m, 1H), 7.23~7.19(m, 1H),
 6.97(d, J=8.9Hz, 1H), 4.86(s, 2H), 3.75(t, J=5.0Hz, 4H),
 2.89(t, J=7.7Hz, 2H), 2.60~2.55(m, 6H), 2.53~2.50(m, 2H),
 2.40(t, J=7.7Hz, 2H), 1.81~1.71(m, 6H), 1.64~1.57(m, 2H),
 1.50~1.44(m, 2H)
 Mass, m/e: 446(M⁺), 157(base)

Example 4-48

In the manner similar to Example 4-1,
 3-amino-7-tert-butyloxycarbonyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)-
 butyl]-5,6,7,8-tetrahydro-3H-pyrido[4',3':4,5]thieno-[2,3-d]pyrimidin-
 4-one was obtained.

¹H-NMR(CDCl₃)δ: 7.88(d, J=9.2Hz, 1H), 7.69(d, J=8.5Hz, 1H),
 7.56~7.60(m, 1H), 7.52(ddd, J=1.5Hz, 6.9Hz, 8.5Hz, 1H),
 7.21(ddd, J=1.5Hz, 6.9Hz, 8.5Hz, 1H), 6.97(d, J=9.3Hz, 1H),
 4.88(s, 2H), 4.60(br s, 2H), 3.68~3.78(m, 6H), 3.00~3.12(m, 4H),
 2.55~2.60(m, 4H), 2.46(t, J=7.0Hz, 2H), 1.82~1.91(m, 2H),
 1.66~1.73(m, 2H), 1.48(s, 9H)
 Mass, m/e: 589(M⁺), 489, 445, 157(base)

Example 4-49

In the manner similar to Example 4-1,
7-acetyl-3-amino-2-[4-(4-quinolin-2-yl)butyl]-5,6,7,8-tetrahydro-3H-pyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4-one was obtained.

5 ¹H-NMR(CDCl₃)δ:7.88(d,J=9.2Hz,1H),7.69(d,J=8.5Hz,1H),
7.58(dd,J=1.1Hz,8.5Hz,1H),
7.52(ddd,J=1.1Hz,6.9Hz,8.5Hz,1H),
7.22(ddd,J=1.1Hz,6.9Hz,8.5Hz,1H),6.97(d,J=9.2Hz,1H),
4.90(br s,2H),4.79(s,2H),3.72~3.80(m,6H),3.13~3.18(m,2H),
10 3.04(t,J=7.0Hz,4H),2.60(t,J=5.0Hz,4H),2.48(t,J=7.0Hz,2H),
2.20(s,3H),1.87(q,J=7.0Hz,2H),1.70(q,J=7.0Hz,2H)
Mass,m/e:531(M⁺),387,157(base)

Example 4-50

15 In the manner similar to Example 4-1,
3-amino-2-[4-(4-quinolin-2-yl)pyperazin-1-yl]butyl]-5,6,7,8-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyrimidin-4-one was obtained.

20 ¹H-NMR(CDCl₃)δ:7.88(d,J=9.2Hz,1H),7.69(d,J=8.5Hz,1H),
7.58(dd,J=1.5Hz,8.5Hz,1H),
7.51(ddd,J=1.5Hz,6.9Hz,8.5Hz,1H),
7.21(ddd,J=1.5Hz,6.9Hz,8.5Hz,1H),6.97(d,J=9.2Hz,1H),
4.87(s,2H),3.73~3.79(m,4H),2.96~3.05(m,4H),
2.75(t,J=5.9Hz,2H),2.58(br s,4H),2.46(t,J=7.3Hz,2H),
25 1.81~1.92(m,6H),1.65~1.74(m,2H)
Mass,m/e:488(M⁺),472,344,157(base)

Example 4-51

30 In the manner similar to Example 4-1,
7-acetyl-3-amino-2-[4-[4-(4-phenylquinolin-2-yl)piperazin-1-yl]butyl]-5,6,7,8-tetrahydro-3H-pyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4-one was obtained.

35 ¹H-NMR(CDCl₃)δ:7.75~7.77(m,2H),
7.70(dd,J=3.1Hz,5.2Hz,1H),7.61(dd,J=1.1Hz,8.5Hz,2),

7.45~7.56(m,4H),7.16(ddd,J=1.1Hz,6.9Hz,8.5Hz,1H),
 4.90(s,2H),3.71~3.83(m,6H),3.15(t,J=5.7Hz,2H),
 3.04(t,J=7.7Hz,4H)2.58(t,J=5.0Hz,4H),2.46(t,J=7.7Hz,2H),
 2.20(s,3H),1.87(q,J=7.7Hz,2H),1.62~1.74(m,2H)
 5 Mass,m/e:607(M⁺),279,149(base)

Example 4-52

In the manner similar to Example 4-1,
 3-amino-6-chloro-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3H-
 10 quinazolin-4-one was obtained.

¹H-NMR(CDCl₃)δ:8.19(d,J=2.3Hz,1H),7.87(d,J=9.2Hz,1H),
 7.68(d,J=9.2Hz,1H),7.66(dd,J=2.3Hz,8.4Hz,1H),
 7.60(d,J=8.4Hz,1H),7.56~7.59(m,1H),
 15 7.52(ddd,J=1.5Hz,6.9Hz,8.5Hz,1H),
 7.21(ddd,J=1.5Hz,6.9Hz,8.5Hz,1H),6.96(d,J=9.2Hz,1H),
 4.90(br s,2H),3.75(t,J=5.0Hz,4H),3.05(t,J=7.4Hz,2H),
 2.58(t,J=5.0Hz,4H),2.47(t,J=7.4Hz,2H),1.89(q,J=7.4Hz,2H),
 1.71(q,J=7.4Hz,2H)
 20 Mass,m/e:462(M⁺),446,157(base)

Example 4-53

In the manner similar to Example 4-1,
 3-amino-6-methoxy-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3H-
 25 quinazolin-4-one was obtained.

¹H-NMR(CDCl₃)δ:7.88(d,J=8.9Hz,1H),7.69(d,J=8.5Hz,1H),
 7.59~7.61(m,1H),7.58(d,J=2.7Hz,1H),
 7.52(ddd,J=1.5Hz,6.9Hz,8.5Hz,1H),7.34(d,J=3.0Hz,1H),
 30 7.32(d,J=2.7Hz,1H),7.21(ddd,J=1.5Hz,6.9Hz,8.5Hz,1H),
 6.97(d,J=1.5Hz,1H),4.92(s,2H),3.19(s,3H),3.73~3.77(4H,m),
 3.05(t,J=7.7Hz,2H),2.58(t,J=7.7Hz,1H),1.89(q,J=7.7Hz,1H),
 1.71(q,J=7.7Hz,1H)
 Mass,m/e:458(M⁺),442,157(base)

Example 4-54

In the manner similar to Example 4-1,
3-amino-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-7-trifluoromethyl-
3H-quinazolin-4-one was obtained.

5

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.35(d, J=8.9Hz, 1H), 7.96(s, 1H),
7.87(d, J=9.2Hz, 1H), 7.67(d, J=8.5Hz, 1H),
7.65(dd, J=1.5Hz, 8.5Hz, 1H), 7.58(dd, J=0.8Hz, 7.7Hz, 1H),
7.52(ddd, J=1.5Hz, 7.0Hz, 8.5Hz, 1H),
10 7.21(ddd, J=1.5Hz, 7.0Hz, 8.5Hz, 1H), 6.96(d, J=9.2Hz, 1H),
4.95(s, 2H), 3.75(t, J=5.0Hz, 4H), 3.09(t, J=7.7Hz, 2H),
2.59(t, J=5.0Hz, 4H), 2.49(t, J=7.7Hz, 2H), 1.92(q, J=7.7Hz, 2H),
1.72(q, J=7.7Hz, 2H)
Mass, m/e: 496(M^+), 480, 157

15

Example 4-55

In the manner similar to Example 4-1,
3-amino-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3H-pyrido-
[3',2':4,5]thieno[3,2-d]pyridin-4-one was obtained.

20

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.75(dd, J=1.5Hz, 4.5Hz, 1H),
8.54(dd, J=1.5Hz, 8.1Hz, 1H), 7.87(d, J=8.9Hz, 1H),
7.67(d, J=8.5Hz, 1H), 7.56~7.60(m, 1H),
7.52(ddd, J=1.5Hz, 7.0Hz, 8.5Hz, 1H), 7.45(dd, J=4.6Hz, 8.1Hz, 1H),
25 7.21(ddd, J=1.5Hz, 7.0Hz, 8.5Hz, 1H), 6.96(d, J=8.9Hz, 1H),
5.09(s, 2H), 3.71~3.79(m, 4H), 3.14(t, J=7.7Hz, 2H),
2.59(t, J=5.0Hz, 4H), 2.50(t, J=7.7Hz, 2H), 1.95(q, J=7.7Hz, 2H),
1.74(q, J=7.7Hz, 2H)
Mass, m/e: 485(M^+), 470, 341, 157(base)

30

Example 4-56

In the manner similar to Example 4-1,
3-amino-6-fluoro-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3H-
quinazolin-4-one was obtained.

35

¹H-NMR(CDCl₃)δ:7.89(d,J=9.2Hz,1H),
 7.87(dd,J=2.7Hz,8.5Hz,1H),7.72~7.65(m,2H),
 7.59(dd,J=1.2Hz,8.1Hz,1H),
 7.53(ddd,J=1.5Hz,6.9Hz,8.5Hz,1H),7.46(dt,J=2.7Hz,8.5Hz,1H),
 5 7.22(ddd,J=1.2Hz,6.9Hz,8.1Hz,1H),6.98(d,J=9.2Hz,1H),
 4.92(s,2H),3.76(t,J=5.0Hz,4H),3.07(t,J=7.7Hz,2H),
 2.59(t,J=5.0Hz,4H),2.49(t,J=7.7Hz,2H),1.91(q,J=7.7Hz,2H),
 1.73(q,J=7.7Hz,2H)
 Mass,m/e:446(M⁺),157(base)

10

Example 4-57

In the manner similar to Example 4-1,
 3-amino-7-fluoro-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3H-
 quinazolin-4-one was obtained.

15

¹H-NMR(CDCl₃)δ:8.25(dd,J=6.2Hz,8.9Hz,1H),
 7.89(d,J=9.2Hz,1H),7.70(d,J=8.1Hz,1H),
 7.59(dd,J=1.2Hz,8.1Hz,1H),
 7.53(ddd,J=1.5Hz,6.9Hz,8.5Hz,1H),
 20 7.31(dd,J=2.7Hz,9.6Hz,1H),
 7.22(ddd,J=1.2Hz,6.9Hz,8.1Hz,1H),
 7.16(dt,J=2.3Hz,8.9Hz,1H),6.98(d,J=9.2Hz,1H),
 4.89(s,2H),3.76(t,J=5.0Hz,4H),3.07(t,J=7.7Hz,2H),
 2.59(t,J=5.0Hz,4H),2.49(t,J=7.7Hz,2H),1.91(q,J=7.7Hz,2H),
 25 1.73(q,J=7.7Hz,2H)
 Mass,m/e:446(M⁺),157(base)

Example 4-58

In the manner similar to Example 4-1,
 30 3-amino-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3H-thieno[3,4-d]-
 pyrimidin-4-one was obtained.

¹H-NMR(DMSO-d₆)δ:8.02(d,J=9.2Hz,1H),7.69(d,J=8.1Hz,1H),
 7.58~7.48(m,2H),7.35~7.28(m,2H),7.25~7.18(m,2H),
 35 5.51(br s,2H),3.68(br s,4H),3.27(br s,2H),2.53~2.24(m,6H),

1.68~1.49(m,4H)

Mass, m/e: 434(M⁺), 157(base)

Example 4-59

5 In the manner similar to Example 4-1,
3-amino-7-methyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-5,6,7,8-
tetrahydro-3H-quinazolin-4-one was obtained.

¹H-NMR(CDCl₃)δ: 7.89(d, J=9.2Hz, 1H), 7.70(d, J=8.5Hz, 1H),
10 7.59(dd, J=1.2Hz, 8.1Hz, 1H),
7.53(ddd, J=1.5Hz, 6.9Hz, 8.5Hz, 1H),
7.22(ddd, J=1.2Hz, 6.9Hz, 8.1Hz, 1H), 6.98(d, J=9.2Hz, 1H),
4.95(s, 2H), 3.76(t, J=5.0Hz, 4H), 2.93(t, J=6.9Hz, 2H),
2.74~2.63(m, 2H), 2.58(t, J=5.0Hz, 4H), 2.49~2.37(m, 3H),
15 2.28~2.18(m, 1H), 1.92~1.75(m, 4H), 1.72~1.59(m, 2H),
1.34~1.22(m, 1H), 1.06(d, J=6.6Hz, 3H)
Mass, m/e: 446(M⁺), 157(base)

Example 4-60

20 In the manner similar to Example 4-1,
3-amino-6-methyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-5,6,7,8-
tetrahydro-3H-quinazolin-4-one was obtained.

¹H-NMR(CDCl₃)δ: 7.89(d, J=9.2Hz, 1H), 7.70(d, J=8.1Hz, 1H),
25 7.59(dd, J=1.2Hz, 8.1Hz, 1H),
7.53(ddd, J=1.5Hz, 6.9Hz, 8.5Hz, 1H),
7.22(ddd, J=1.2Hz, 6.9Hz, 8.1Hz, 1H),
6.98(d, J=9.2Hz, 1H), 4.95(s, 2H), 3.76(t, J=5.0Hz, 4H),
2.93(t, J=7.7Hz, 2H), 2.77~2.69(m, 1H), 2.67~2.60(m, 2H),
30 2.58(t, J=5.0Hz, 4H), 2.45(t, J=7.3Hz, 2H), 2.09~1.98(m, 1H),
1.92~1.62(m, 6H), 1.45~1.32(m, 1H), 1.08(d, J=6.6Hz, 3H)
Mass, m/e: 446(M⁺), 157(base)

Example 4-61

35 In the manner similar to Example 4-1,

3-amino-6-ethyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-5,6,7,8-tetrahydro-3H-quinazolin-4-one was obtained.

¹H-NMR(CDCl₃)δ: 7.89(d, J=9.2Hz, 1H), 7.70(d, J=8.5Hz, 1H),
 5 7.59(d, J=8.1Hz, 1H), 7.53(t, J=8.1Hz, 1H), 7.22(t, J=8.1Hz, 1H),
 6.98(d, J=9.2Hz, 1H), 4.95(s, 2H), 3.76(t, J=5.0Hz, 4H),
 2.93(t, J=7.3Hz, 2H), 2.80~2.72(m, 1H), 2.66~2.53(m, 6H),
 2.45(t, J=7.3Hz, 2H), 2.09~1.98(m, 1H), 1.98~1.89(m, 1H),
 1.81(q, J=7.3Hz, 2H), 1.72~1.30(m, 6H), 0.98(t, J=7.3Hz, 3H)
 10 Mass, m/e: 460(M⁺), 157(base)

Example 4-62

In the manner similar to Example 4-1,
 3-amino-6,7-dimethyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-
 15 5,6,7,8-tetrahydro-3H-quinazolin-4-one was obtained.

¹H-NMR(CDCl₃)δ: 7.89(d, J=9.2Hz, 1H), 7.70(d, J=8.5Hz, 1H),
 7.59(dd, J=1.2Hz, 8.1Hz, 1H),
 7.53(ddd, J=1.5Hz, 6.9Hz, 8.1Hz, 1H),
 20 7.22(ddd, J=1.2Hz, 6.9Hz, 8.1Hz, 1H), 6.98(d, J=9.2Hz, 1H),
 4.95(s, 2H), 3.76(t, J=5.0Hz, 4H), 3.00~2.86(m, 2H),
 2.73~2.52(m, 6H), 2.45(t, J=7.3Hz, 2H), 2.40~2.25(m, 2H),
 2.04~1.90(m, 2H), 1.86~1.76(m, 2H), 1.73~1.59(m, 2H),
 0.95~0.89(m, 6H)
 25 Mass, m/e: 460(M⁺), 157(base)

Example 4-63

In the manner similar to Example 4-1,
 3-amino-6-tert-butyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-5,6,7,8-
 30 tetrahydro-3H-quinazolin-4-one was obtained.

¹H-NMR(CDCl₃)δ: 7.89(d, J=9.2Hz, 1H), 7.70(d, J=8.5Hz, 1H),
 7.59(dd, J=1.2Hz, 8.1Hz, 1H),
 7.53(ddd, J=1.5Hz, 6.9Hz, 8.5Hz, 1H),
 35 7.22(ddd, J=1.2Hz, 6.9Hz, 8.1Hz, 1H), 6.98(d, J=9.2Hz, 1H),

4.96(s,2H),3.76(t,J=5.0Hz,4H),2.94(t,J=7.7Hz,2H),
 2.76~2.54(m,7H),2.45(t,J=7.3Hz,2H),2.20~2.10(m,1H),
 2.04~1.96(m,1H),1.86~1.76(m,2H),1.72~1.57(m,2H),
 1.39~1.23(m,2H),0.96(s,9H)
 5 Mass,m/e:488(M⁺),157(base)

Example 4-64

In the manner similar to Example 4-1,
 3-amino-5,7,7-trimethyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-
 10 5,6,7,8-tetrahydro-3H-quinazolin-4-one was obtained.

¹H-NMR(CDCl₃)δ:7.89(d,J=9.2Hz,1H),7.70(d,J=8.5Hz,1H),
 7.59(dd,J=1.2Hz,8.1Hz,1H),
 7.53(ddd,J=1.5Hz,6.9Hz,8.5Hz,1H),
 15 7.22(ddd,J=1.2Hz,6.9Hz,8.1Hz,1H),6.98(d,J=9.2Hz,1H),
 4.94(s,2H),3.76(t,J=5.0Hz,4H),3.00~2.80(m,3H),
 2.58(t,J=5.0Hz,4H),2.52~2.42(m,3H),2.32~2.25(m,1H),
 1.87~1.62(m,5H),1.33(d,J=6.6Hz,3H),1.23~1.15(m,1H),
 1.06(s,3H),0.85(s,3H)
 20 Mass,m/e:474(M⁺),157(base)

Example 4-65

In the manner similar to Example 4-1,
 3-amino-2-[4-(4-benzothiazol-2-ylpiperazin-1-yl)butyl]-5,6,7,8-
 25 tetrahydro-3H-quinazolin-4-one was obtained.

¹H-NMR(CDCl₃)δ:7.60(d,J=8.5Hz,1H),7.55(d,J=8.1Hz,1H),
 7.32~7.27(m,1H),7.10~7.04(m,1H),4.90(s,2H),
 3.65(t,J=5.0Hz,4H),2.92(t,J=7.7Hz,2H),2.62~2.49(m,8H),
 30 2.45(t,J=7.3Hz,2H),1.85~1.60(m,8H)
 Mass,m/e:438(M⁺),422(base)

Example 4-66

In the manner similar to Example 4-1,
 35 3-amino-6,6-ethylenedioxy-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-

5,6,7,8-tetrahydro-3H-quinazolin-4-one was obtained.

¹H-NMR(CDCl₃)δ: 7.89(d, J=9.2Hz, 1H), 7.70(d, J=8.1Hz, 1H),
 7.59(dd, J=1.2Hz, 7.7Hz, 1H),
 5 7.53(ddd, J=1.5Hz, 6.9Hz, 8.1Hz, 1H),
 7.22(ddd, J=1.2Hz, 6.9Hz, 8.1Hz, 1H), 6.98(d, J=9.2Hz, 1H),
 4.94(s, 2H), 4.07~3.98(m, 4H), 3.76(t, J=5.0Hz, 4H),
 2.94(t, J=7.7Hz, 2H), 2.85(t, J=6.9Hz, 2H), 2.75(s, 2H),
 2.58(t, J=5.0Hz, 4H), 2.45(t, J=7.3Hz, 2H), 1.96(t, J=6.9Hz, 2H),
 10 1.80(q, J=7.7Hz, 2H), 1.72~1.59(m, 2H)
 Mass, m/e: 490(M⁺), 157(base)

Example 4-67

To a mixed solution of 29 ml of acetone and 1 ml of water, 229
 15 mg of 3-amino-6,6-ethylenedioxy-2-[4-(4-quinolin-2-ylpiperazin-
 1-yl)butyl]-5,6,7,8-tetrahydro-3H-quinazolin-4-one as synthesized in
 Example 4-66 and 59 mg of pyridinium p-toluenesulfonate were
 added and heated under reflux for 112 hours. After cooling, the
 reaction mixture was extracted with methylene chloride, washed
 20 with water, dried over anhydrous magnesium sulfate, and the solvent
 was distilled off under reduced pressure. Purifying the residue on
 silica gel column chromatography (methanol : methylene chloride =
 1:9) to provide 194 mg (78%) of 6,6-ethylenedioxy-3-
 isopropylideneamino-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-
 25 5,6,7,8-tetrahydro-3H-quinazolin-4-one.

¹H-NMR(CDCl₃)δ: 7.89(d, J=9.2Hz, 1H), 7.70(d, J=8.5Hz, 1H),
 7.59(dd, J=1.2Hz, 8.5Hz, 1H),
 7.53(ddd, J=1.5Hz, 6.9Hz, 8.5Hz, 1H),
 30 7.22(ddd, J=1.2Hz, 6.9Hz, 8.1Hz, 1H), 6.98(d, J=9.2Hz, 1H),
 4.08~3.99(m, 4H), 3.76(t, J=5.0Hz, 4H), 2.86(t, J=6.6Hz, 2H),
 2.75(br s, 2H), 2.63(t, J=7.3Hz, 2H), 2.57(t, J=5.0Hz, 4H),
 2.45~2.37(m, 2H), 1.97(t, J=6.9Hz, 2H), 1.66~1.57(m, 2H),
 1.59(s, 6H), 1.31~1.24(m, 2H)
 35 Mass, m/e: 530(M⁺), 157(base)

Example 4-68

To 10 ml of methanol, 300 mg of sodium borohydride was added and into this mixture, a solution of 145 mg of
 5 6,6-ethylenedioxy-3-isopropylideneamino-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-5,6,7,8-tetrahydro-3H-quinazolin-4-one as synthesized in Example 4-67 in 10 ml of methanol was dropped under cooling with ice. Raising the temperature to room temperature, the reaction mixture was stirred for an hour. Distilling the system
 10 under reduced pressure, water was added to the distillation residue, extracted with methylene chloride, washed with water, dried over anhydrous magnesium sulfate and the solvent was distilled off under reduced pressure. The residue was purified on silica gel column chromatography (methanol : methylene chloride = 2:23) to provide 89
 15 mg (61%) of 6,6-ethylenedioxy-3-isopropylamino-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-5,6,7,8-tetrahydro-3H-quinazolin-4-one.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.89(d, J=9.2Hz, 1H), 7.70(d, J=8.5Hz, 1H),
 7.59(dd, J=1.2Hz, 8.1Hz, 1H),
 20 7.53(ddd, J=1.5Hz, 6.9Hz, 8.5Hz, 1H),
 7.22(ddd, J=1.2Hz, 6.9Hz, 8.1Hz, 1H), 6.98(d, J=9.2Hz, 1H),
 5.33(d, J=4.6Hz, 1H), 4.09~3.99(m, 4H), 3.76(t, J=5.0Hz, 4H),
 3.41~3.32(m, 1H), 2.84(t, J=6.6Hz, 2H), 2.74(s, 2H),
 2.58(t, J=5.0Hz, 4H), 2.43(t, J=7.3Hz, 2H), 1.96(t, J=6.6Hz, 2H),
 25 1.82~1.72(m, 2H), 1.67~1.56(m, 4H), 1.16~1.01(m, 6H)
 Mass, m/e: 532(M^+), 157(base)

Example 4-69

To 40 ml of 6N-hydrochloric acid, 2.72 g of 3-amino-6,6-
 30 ethylenedioxy-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-5,6,7,8-tetrahydro-3H-quinazolin-4-one as synthesized in Example 4-66 was added and heated under reflux for an hour. After cooling, the reaction mixture was neutralized with saturated aqueous sodium hydrogencarbonate solution, extracted with methylene chloride, dried
 35 over anhydrous magnesium sulfate, and the solvent was distilled off

under reduced pressure. The residue was purified on silica gel column chromatography (methanol : methylene chloride = 2:23) to provide 1.77 g (71%) of 3-amino-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3,4,5,6,7,8-hexahydro-4,6-dioxaquinazoline.

5

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.89(d, J=9.2Hz, 1H), 7.70(d, J=8.5Hz, 1H),
 7.60(dd, J=1.2Hz, 8.1Hz, 1H),
 7.53(ddd, J=1.5Hz, 6.9Hz, 8.5Hz, 1H),
 7.23(ddd, J=1.2Hz, 6.9Hz, 8.1Hz, 1H),
 6.98(d, J=9.2Hz, 1H), 5.01(s, 2H), 3.76(t, J=5.0Hz, 4H),
 3.39(s, 2H), 3.06~2.95(m, 4H), 2.66(t, J=7.3Hz, 2H),
 2.59(t, J=5.0Hz, 4H), 2.47(t, J=7.3Hz, 2H), 1.89~1.79(m, 2H),
 1.74~1.64(m, 2H)
 Mass, m/e: 446(M^+), 157(base)

15

Example 4-70

To 25 ml of methanol, 500 mg of sodium borohydride was added, and into this mixture, a solution of 1.00 g of 3-amino-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3,4,5,6,7,8-hexahydro-4,6-dioxaquinazoline as synthesized in Example 4-69 in 25 ml of methanol was dropped under cooling with ice. Raising the temperature to room temperature, the system was stirred for 3 hours, followed by distillation under reduced pressure. After addition of water, the distillation residue was extracted with methylene chloride, washed with water, dried over anhydrous magnesium sulfate and the solvent was distilled off under reduced pressure. The residue was purified on silica gel column chromatography (methanol : methylene chloride = 1:9) to provide 520 mg (52%) of 3-amino-6-hydroxy-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-5,6,7,8-tetrahydro-3H-quinazolin-4-one.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.88(d, J=9.2Hz, 1H), 7.70(d, J=8.5Hz, 1H),
 7.59(d, J=8.1Hz, 1H), 7.53(ddd, J=1.5Hz, 6.9Hz, 8.5Hz, 1H),
 7.22(ddd, J=1.2Hz, 6.9Hz, 8.1Hz, 1H), 6.97(d, J=9.2Hz, 1H),
 4.97(s, 2H), 4.24~4.16(m, 1H), 3.75(t, J=5.0Hz, 4H),

35

2.93(t, J=7.7Hz, 2H), 2.88~2.76(m, 2H), 2.69~2.49(m, 6H),
 2.45(t, J=7.3Hz, 2H), 2.01~1.61(m, 6H)
 Mass, m/e: 448(M⁺), 157(base)

5 Example 4-71

In the manner similar to Example 4-1,
 3-amino-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-6-trifluoromethyl-
 5,6,7,8-tetrahydro-3H-quinazolin-4-one was obtained.

10 ¹H-NMR(CDCl₃) δ: 7.89(d, J=9.2Hz, 1H), 7.70(d, J=8.5Hz, 1H),
 7.59(dd, J=1.2Hz, 8.1Hz, 1H),
 7.53(ddd, J=1.5Hz, 6.9Hz, 8.5Hz, 1H),
 7.23(ddd, J=1.2Hz, 6.9Hz, 8.1Hz, 1H), 6.98(d, J=9.2Hz, 1H),
 4.97(s, 2H), 3.79~3.74(m, 4H), 2.98~2.90(m, 3H),
 15 2.82~2.32(m, 10H), 2.23~2.15(m, 1H), 1.86~1.62(m, 5H)
 Mass, m/e: 500(M⁺), 157(base)

Example 5: Syntheses of compounds of the formula (I) in which X¹
 stands for hydrogen and Y stands for nitrogen

20 Example 5-1

Step 5-1-A: To 14 ml of methanol, 256 mg of sodium was added at
 room temperature under stirring, then 1.04 g of nitroguanidine was
 added, followed by 45 minutes' heating under reflux. Successively,
 1.70 g of ethyl 2-cyclohexanonecarboxylate was added, followed by 9
 25 hours' heating under reflux. After cooling the reaction mixture, the
 solvent was distilled off under reduced pressure. Water was added
 to the residue, and the system was acidified with acetic acid. The
 precipitate was recovered by filtration and dried to provide 1.76 g
 (84%) of 2-nitroamino-5,6,7,8-tetrahydro-3H-quinazolin-4-one.

30

¹H-NMR(DMSO-d₆) δ: 2.56~2.45(m, 2H) 2.30~2.19(m, 2H),
 1.74~1.58(m, 4H)
 Mass, m/e: 210((M+1)⁺), 122(base)

35 Step 5-1-B: To a solution of 1.52 g of 2-[3-(4-quinolin-2-ylpiperazin-1-

yl)propyl]isoindol-1,3-dione in 30 ml of ethanol, another solution of 1.50 g of hydrazine monohydrate in 10 ml of ethanol was added, and heated under reflux for 7 hours. Cooling the reaction mixture, insoluble matter was separated by filtration, and the solvent was
 5 distilled off under reduced pressure. The residue was made alkaline with 5N-sodium hydroxide, extracted with chloroform, washed with saturated brine and dried over anhydrous sodium sulfate. Distilling the solvent off under reduced pressure, 0.99 g (96%) of
 3-(4-quinolin-2-ylpiperazin-1-yl)propylamine was obtained.

10

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.87(d, J=8.9Hz, 1H), 7.69(d, J=8.5Hz, 1H),
 7.58(d, J=8.1Hz, 1H), 7.52(ddd, J=1.5Hz, 6.9Hz, 8.5Hz, 1H),
 7.23(ddd, J=1.2Hz, 6.9Hz, 8.1Hz, 1H), 6.97(d, J=8.9Hz, 1H),
 3.75(t, J=5.4Hz, 4H), 2.78(t, J=6.9Hz, 2H), 2.58(t, J=5.4Hz, 4H),
 15 2.46(t, J=7.3Hz, 2H), 1.78~1.63(m, 2H)
 Mass, m/e: 270(M^+), 157(base)

Step 5-1-C: To 3 ml of pyridine, 210 mg of 2-nitroamino-5,6,7,8-tetrahydro-3H-quinazolin-4-one as obtained in above Step 5-1-A and
 20 270 mg of 3-(4-quinolin-2-ylpiperazin-1-yl)propylamine as obtained in above step 5-1-B were added and heated under reflux for 16 hours. Cooling the system, the solvent was distilled off under reduced pressure. The residue was purified on silica gel column chromatography (25% aqueous ammonia : methanol : chloroform =
 25 0.5:5:45) to provide 301 mg (72%) of 2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylamino]-5,6,7,8-tetrahydro-3H-quinazolin-4-one.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.87(d, J=8.9Hz, 1H), 7.68(d, J=8.1Hz, 1H),
 7.58(d, J=7.8Hz, 1H), 7.52(t, J=7.0Hz, 1H), 7.21(t, J=7.0Hz, 1H),
 30 6.97(d, J=9.2Hz, 1H), 5.73(br s, 1H), 3.91(br s, 4H),
 3.39(br s, 2H), 2.62(t, J=5.0Hz, 4H), 2.51(t, J=6.2Hz, 2H),
 2.42(t, J=6.2Hz, 2H), 2.37(t, J=6.2Hz, 2H), 1.98~1.53(m, 6H)
 Mass, m/e: 418(M^+), 157(base)

35 Example 5-2

In the manner similar to Example 5-1,
2-[4-(4-quinolin-2-ylpiperazin-1-yl)butylamino]-5,6,7,8-tetrahydro-
3H-quinazolin-4-one was obtained.

5 $^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.87(d, J=9.2Hz, 1H), 7.68(d, J=8.5Hz, 1H),
7.58(d, J=8.1Hz, 1H), 7.52(ddd, J=1.5Hz, 6.9Hz, 8.5Hz, 1H),
7.21(t, J=8.1Hz, 1H), 6.96(d, J=9.2Hz, 1H), 6.05(br s, 1H),
3.76(t, J=5.0Hz, 4H), 3.38(br s, 2H), 2.58(t, J=5.0Hz, 4H),
2.52~2.28(m, 6H), 1.95~1.51(m, 8H)
10 Mass, m/e: 432(M^+), 157(base)

Example 5-3

In the manner similar to Example 5-1,
2-[3-[4-(4-methylquinolin-2-yl)piperazin-1-yl]propylamino]-5,6,7,8-
15 tetrahydro-3H-quinazolin-4-one was obtained.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.77(d, J=8.5Hz, 1H), 7.69(d, J=7.7Hz, 1H),
7.52(ddd, J=1.5Hz, 6.9Hz, 8.5Hz, 1H), 7.24(t, J=7.7Hz, 1H),
6.84(s, 1H), 3.95(br s, 4H), 3.39(br s, 2H), 2.62(t, J=5.0Hz, 4H),
20 2.59(s, 3H), 2.52(t, J=6.2Hz, 2H), 2.46~2.36(m, 4H),
1.87~1.64(m, 6H)
Mass, m/e: 432(M^+), 171(base)

Example 5-4

25 In the manner similar to Example 5-1,
2-[3-[4-(7-methoxyisoquinolin-1-yl)piperazin-1-yl]propylamino]-
5,6,7,8-tetrahydro-3H-quinazolin-4-one was obtained.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.04(d, J=5.8Hz, 1H), 7.66(d, J=8.9Hz, 1H),
30 7.37(d, J=2.7Hz, 1H), 7.27(dd, J=2.7Hz, 8.9Hz, 1H),
7.20(d, J=5.8Hz, 1H), 6.00(br s, 1H), 3.93(s, 3H), 3.56(br s, 4H),
3.41(br s, 2H), 2.77(br s, 4H), 2.59(t, J=6.2Hz, 2H),
2.48~2.41(m, 2H), 2.40~2.33(m, 2H), 1.91~1.80(m, 2H),
1.78~1.63(m, 4H)
35 Mass, m/e: 448(M^+), 187(base)

Example 5-5

In the manner similar to Example 5-1,

2-[3-(4-pyrrolo[1,2-a]quinoxalin-4-ylpiperazin-1-yl)propylamino]-
5 5,6,7,8-tetrahydro-3H-quinazolin-4-one was obtained.

¹H-NMR(CDCl₃)δ:7.81(dd,J=1.2Hz,2.7Hz,1H),
7.72(dd,J=1.5Hz,8.1Hz,1H),7.65(dd,J=1.5Hz,7.7Hz,1H),
7.35~7.23(m,2H),6.80~6.73(m,2H),4.01(br s,4H),
10 3.40(br s,2H),3.69(t,J=5.0Hz,4H),2.54(t,J=6.2Hz,2H),
2.44(t,J=5.7Hz,2H),2.39(t,J=5.7Hz,2H),1.88~1.63(m,6H)
Mass,m/e:457(M⁺),196(base)

Example 5-6

15 In the manner similar to Example 5-1,

2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylamino]-3H-quinazolin-4-one
was obtained.

¹H-NMR(CDCl₃)δ:8.09(br s,1H),7.90(d,J=9.2Hz,1H),
20 7.71(d,J=8.5Hz,1H),7.61(d,J=8.1Hz,1H),7.58~7.51(m,2H),
7.38~7.19(m,2H),7.15(br s,1H),6.99(d,J=9.2Hz,1H),
3.92(t,J=5.0Hz,4H),3.55(br s,2H),2.67(br s,4H),
2.60(t,J=6.2Hz,2H),1.95(br s,2H)
Mass,m/e:414(M⁺),157(base)

25

Example 5-7

In the manner similar to Example 5-1,

2-[3-[4-(7-methoxyisoquinolin-1-yl)piperazin-1-yl]propylamino]-3H-
quinazolin-4-one was obtained.

30

¹H-NMR(CDCl₃)δ:8.13~8.03(m,2H),7.69(d,J=8.9Hz,1H),
7.55(ddd,J=1.5Hz,6.9Hz,8.5Hz,1H),7.39(d,J=2.3Hz,1H),
7.35(d,J=8.1Hz,1H),7.29(dd,J=2.3Hz,8.1Hz,1H),
7.27~7.21(m,1H),7.14(br s,1H),3.93(s,3H),3.62~3.53(m,6H),
35 2.83(br s,4H),2.69(t,J=6.2Hz,2H),2.07~1.94(m,2H)

Mass, m/e: 444(M⁺), 187(base)

Example 5-8

In the manner similar to Example 5-1,

- 5 2-[3-(4-pyrrolo[1,2-a]quinoxalin-4-yl)piperazin-1-yl]propylamino]-3H-quinazolin-4-one was obtained.

¹H-NMR(CDCl₃) δ: 8.09(br s, 1H), 7.82(s, 1H),
 7.74(d, J=7.7Hz, 1H), 7.68(d, J=7.7Hz, 1H),
 10 7.56(ddd, J=1.5Hz, 6.9Hz, 8.5Hz, 1H), 7.38~7.24(m, 3H),
 7.12(br s, 1H), 6.81~6.73(m, 2H), 3.99(br s, 4H),
 3.56(br s, 2H), 2.73(br s, 4H), 2.62(t, J=6.2Hz, 2H), 1.95(br s, 2H)
 Mass, m/e: 453(M⁺), 196(base)

- 15 Example 6: Syntheses of compounds of the formula (I) in which X¹ stands for amino, lower alkylamino, di-lower alkylamino or lower alkylideneamino, and Y stands for nitrogen

Example 6-1

Step 6-1-A: To a solution 209 mg of potassium

- 20 3-amino-3H-quinazolin-4-one-2-thiolate in 5 ml of dimethylformamide, 141 mg of methyl iodide was added, and stirred for 20 minutes at room temperature. Water was added to the solution, followed by extraction with ethyl acetate and drying over anhydrous magnesium sulfate. Distilling the solvent off under
 25 reduced pressure, 161 mg (86%) of 3-amino-2-methylthio-3H-quinazolin-4-one was obtained.

Step 6-1-B: A mixture of 131 mg of 3-amino-2-methylthio-3H-

- 30 quinazolin-4-one as synthesized in above Step 6-1-A and 172 mg 3-(4-quinolin-2-yl)piperazin-1-yl)propylamine was heated at 145°C under stirring for 5 hours. The reaction mixture was cooled and purified on silica gel column chromatography (methanol : methylene chloride = 1:19) to provide 198 mg (73%) of 3-amino-2-[3-(4-quinolin-2-yl)piperazin-1-yl]propylamino]-3H-quinazolin-4-one.

¹H-NMR(CDCl₃)δ:8.06(dd,J=1.5Hz,8.1Hz,1H),
 7.90(d,J=9.2Hz,1H),7.71(d,J=8.1Hz,1H),7.62~7.51(m,3H),
 7.50~7.45(m,1H),7.37(d,J=8.1Hz,1H),
 7.23(ddd,J=1.2Hz,6.9Hz,8.1Hz,1H),
 5 7.13(ddd,J=1.2Hz,6.9Hz,8.1Hz,1H),6.99(d,J=9.2Hz,1H),
 4.51(s,2H),3.81(t,J=5.0Hz,4H),3.64(q,J=6.2Hz,2H),
 2.65(t,J=5.0Hz,4H),2.60(t,J=6.2Hz,2H),1.91(q,J=6.2Hz,2H)
 Mass,m/e:429(M⁺),157(base)

10 Example 6-2

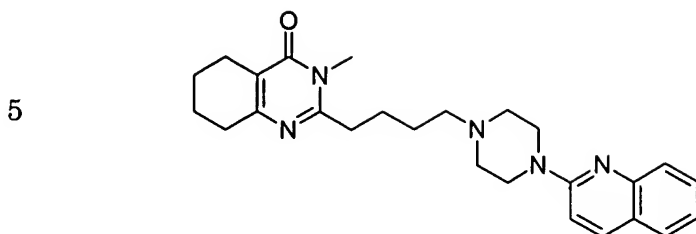
In the manner similar to Example 6-1,
 3-amino-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylamino]-5,6,7,8-
 tetrahydro-3H-quinazolin-4-one was obtained.

15 ¹H-NMR(CDCl₃)δ:7.90(d,J=9.2Hz,1H),7.70(d,J=8.5Hz,1H),
 7.60(dd,J=1.2Hz,8.1Hz,1H),
 7.53(ddd,J=1.5Hz,6.9Hz,8.5Hz,1H),
 7.23(ddd,J=1.2Hz,6.9Hz,8.1Hz,1H),6.98(d,J=9.2Hz,1H),
 4.42(br s,2H),3.80(t,J=5.0Hz,4H),3.52(q,J=6.2Hz,2H),
 20 2.63(t,J=5.0Hz,4H),2.56(t,J=6.2Hz,2H),2.50~2.40(m,4H),
 1.89~1.80(m,2H),1.78~1.66(m,4H)
 Mass,m/e:433(M⁺),157(base)

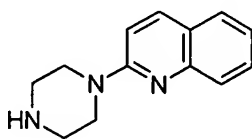
Example 6-3

25 In the manner similar to Example 6-1,
 3-amino-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylamino]-5,6,7,8-
 tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyrimidin-4-one was obtained.

30 ¹H-NMR(CDCl₃)δ:7.90(d,J=9.2Hz,1H),7.70(d,J=8.5Hz,1H),
 7.60(d,J=7.7Hz,1H),7.54(ddd,J=1.2Hz,6.9Hz,8.1Hz,1H),
 7.46~7.41(m,1H),7.23(ddd,J=1.2Hz,6.9Hz,8.1Hz,1H),
 6.99(d,J=9.2Hz,1H),4.41(s,2H),3.81(t,J=5.0Hz,4H),
 3.57(q,J=5.8Hz,2H),2.93~2.88(m,2H),2.69~2.55(m,8H),
 1.92~1.76(m,6H)
 35 Mass,m/e:489(M⁺),157(base)

Example 7-1Step 7-1-A: Synthesis of 2-piperazin-1-ylquinoline

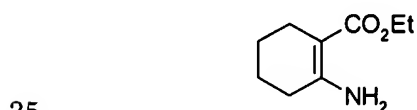
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To a solution formed by dissolving 4.31 g of anhydrous
 15 piperazine in 30 ml of ethylene glycol, 818 mg of 2-chloroquinoline
 was added, and stirred at 140°C for 2 hours. After cooling the
 reaction mixture, saturated aqueous sodium hydrogencarbonate
 solution was added, followed by extraction with chloroform. The
 organic layer was dried over anhydrous magnesium sulfate, and
 20 concentrated under reduced pressure. The residue was purified on
 silica gel column chromatography (chloroform : methanol = 2:1) to
 provide 1.09 g (100%) of 2-piperazin-1-ylquinoline.

¹H-NMR(CDCl₃)δ:7.89(d,J=9.2Hz,1H),7.70(d,J=8.4Hz,1H),
 25 7.59(dd,J=1.5Hz,8.0Hz,1H),
 7.53(ddd,J=1.5Hz,7.0Hz,8.4Hz,1H),7.26~7.22(m,1H),
 6.97(d,J=9.2Hz,1H),3.70(t,J=5.0Hz,4H),3.01(t,J=5.0Hz,4H)
 Mass,m/e:213(M⁺),145(base)

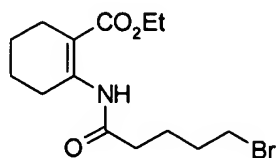
30 Step 7-1-B: Synthesis of 2-aminocyclohex-1-enecarboxylic acid ethyl
ester



To 7N-ammonia-methanol solution, 170 g of ethyl 2-oxocyclohexanecarboxylate was added and stirred for an overnight at room temperature. Concentrating the solvent under reduced pressure, crude crystals were obtained, which were recrystallized from ethyl acetate-n-hexane to provide 152 g (90%) of 2-aminocyclohex-1-enecarboxylic acid ethyl ester.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 4.14(q, J=7.3Hz, 2H), 2.25(d, J=5.9Hz, 2H), 2.20(d, J=5.9Hz, 2H), 1.67~1.56(m, 4H)
Mass, m/e: 169(M^+), 96(base)

Step 7-1-C: Synthesis of 2-(5-bromopentanoylamino)cyclohex-1-enecarboxylic acid ethyl ester



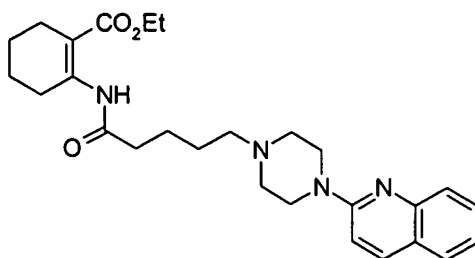
In 150 ml of tetrahydrofuran, 42.3 g of ethyl 2-aminocyclohex-1-enecarboxylate as synthesized in above Step 7-1-B was dissolved, to which 40 g of pyridine was added, and then 5-bromovaleryl chloride was dropped thereinto under cooling with ice. Stirring the system for an overnight at room temperature, ethyl acetate was added, followed by washing with saturated aqueous sodium hydrogencarbonate solution, 10% aqueous citric acid and saturated brine, and drying over anhydrous magnesium sulfate. Concentrating the solvent under reduced pressure, the residue was purified on silica gel column chromatography (n-hexane : ethyl acetate = 8:1) to provide 76.6 g (92%) of 2-(5-bromopentanoylamino)-cyclohex-1-enecarboxylic acid ethyl ester.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 11.62(br s, 1H), 4.22~4.09(m, 2H), 3.42(t, J=6.9Hz, 2H), 2.97~2.94(m, 2H), 2.34(t, J=7.0Hz, 2H), 2.32~2.23(m, 2H), 1.94~1.88(m, 2H), 1.85~1.79(m, 2H), 1.65~1.56(m, 4H), 1.30(t, J=7.0Hz, 3H)

Mass, m/e: 333(M⁺), 55(base)

Step 7-1-D: Synthesis of 2-[5-(4-quinolin-2-ylpiperazin-1-yl)pentanoylamino]cyclohex-1-enecarboxylic acid ethyl ester

5



10

A mixture of 66.5 g of 2-(5-bromopentanoylamino)cyclohex-1-enecarboxylic acid ethyl ester as synthesized in above Step 7-1-C, 46.9 g of 2-piperazin-1-ylquinoline as synthesized in above Step 7-1-A, 22.3 g of triethylamine and 350 ml of toluene was heated under reflux for an overnight. The solvent was concentrated under reduced pressure, and ethyl acetate was added to the residue, followed by washing with saturated aqueous sodium hydrogencarbonate solution. The organic layer was dried over anhydrous magnesium sulfate and the solvent was concentrated under reduced pressure. The residue was purified on silica gel column chromatography (n-hexane : ethyl acetate : methanol = 1:6:0.2) to provide 79.8 g (86%) of 2-[5-(4-quinolin-2-ylpiperazin-1-yl)pentanoylamino]cyclohex-1-enecarboxylic acid ethyl ester.

25

¹H-NMR(CDCl₃) δ: 11.61(br s, 1H), 7.87(d, J=9.2Hz, 1H), 7.69(d, J=8.5Hz, 1H), 7.58~7.56(m, 1H), 7.51(ddd, J=1.5Hz, 6.9Hz, 8.5Hz, 1H), 7.20(ddd, J=1.2Hz, 6.9Hz, 8.1Hz, 1H), 6.97(d, J=9.2Hz, 1H), 4.16(q, J=6.9Hz, 2H), 3.74(t, J=5.0Hz, 4H), 2.97(t, J=5.0Hz, 2H), 2.56(t, J=5.0Hz, 4H), 2.43~2.90(m, 6H), 1.74~1.70(m, 2H), 1.68(m, 4H), 1.28(t, J=6.9Hz, 2H)
Mass, m/e: 464(M⁺), 157(base)

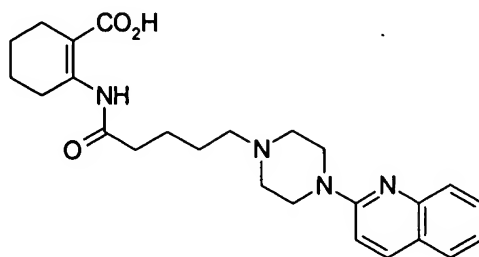
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Step 7-1-E: Synthesis of 2-[5-(4-quinolin-2-ylpiperazin-1-yl)-

35

pentanoylamino]cyclohex-1-enecarboxylic acid

5

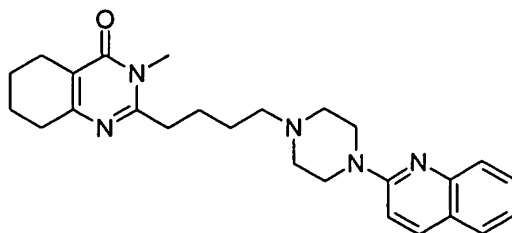


10 In 725 ml of 2-propanol and 365 ml of distilled water, 168.0 g of ethyl 2-[5-(4-quinolin-2-ylpiperazin-1-yl)pentanoylamino]cyclohex-1-enecarboxylate as synthesized in above Step 7-1-D was suspended. To the suspension 580 ml of 1N-aqueous sodium hydroxide was added and heated under reflux for 1.5 hours. After cooling, the reaction mixture was neutralized with 2N-hydrochloric acid. Whereupon
15 precipitated crystals were recovered by filtration and dried to provide 131.8 g (83.4%) of 2-[5-(4-quinolin-2-ylpiperazin-1-yl)pentanoylamino]cyclohex-1-enecarboxylic acid.

20 ¹H-NMR(CDCl₃)δ:12.29(br s,1H),7.92(d,J=9.2Hz,1H),7.70(d,J=8.5Hz,1H),7.61(d,J=8.1Hz,1H),7.57~7.53(m,1H),7.18~7.15(m,1H),6.96(d,J=8.9Hz,1H),3.89(br s,4H),2.92~2.91(m,6H),2.72~2.69(m,2H),2.37~2.35(m,2H),2.32~2.31(m,2H),1.73~1.67(m,4H),1.61~1.55(m,4H)
25 Mass,m/e:418(M⁺-18),392(M⁺-44),157(base)

Step 7-1-F: Synthesis of 3-methyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)-butyl]-5,6,7,8-tetrahydro-3H-quinazolin-4-one

30

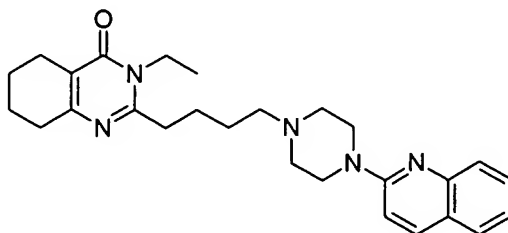


35 In 30 ml of tetrahydrofuran, 10.0 g of 2-[5-(4-quinolin-2-

ylpiperazin-1-yl)-pentanoylamino]cyclohex-1-enecarboxylic acid as synthesized in above Step 7-1-E was suspended, and to the suspension, 7.0 g of 3 equivalent of acetic anhydride was added, followed by an hour's heating under reflux. The solution was cooled with ice, and while continuing the cooling, 35.6 ml of excessive 40% methylamine-methanol solution was gradually added. After about 10 minutes' refluxing under stirring, the temperature was cooled to room temperature and the solution was concentrated under reduced pressure. After addition of 80 ml of distilled water and 30 minutes' stirring, precipitated crystals were recovered by filtration and dried to provide 8.83 g (89.3%) of 3-methyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-5,6,7,8-tetrahydro-3H-quinazolin-4-one.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.88(d, J=9.1Hz, 1H), 7.69(d, J=8.5Hz, 1H), 7.58(d, J=8.1Hz, 1H), 7.52(dd, J=8.5Hz, J=1.5Hz, 1H), 7.23~7.20(m, 1H), 6.97(d, J=9.2Hz, 1H), 3.75(br s, 4H), 3.53(s, 3H), 2.74(t, J=7.7Hz, 2H), 2.57~2.54(m, 6H), 2.50~2.43(m, 4H), 1.83~1.66(m, 8H)
Mass, m/e: 431(M^+), 157(base)

Example 7-2

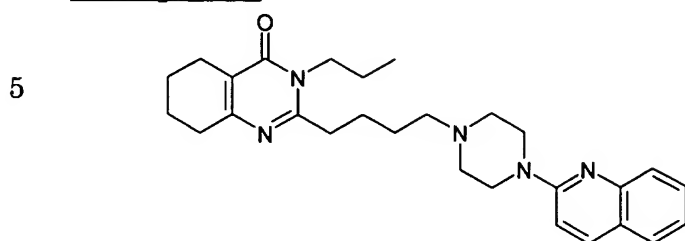


In the manner similar to Example 7-1, 3-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-5,6,7,8-tetrahydro-3H-quinazolin-4-one was synthesized.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.88(d, J=8.9Hz, 1H), 7.69(d, J=8.5Hz, 1H), 7.58(d, J=8.1Hz, 1H), 7.54~7.50(m, 1H), 7.23~7.19(m, 1H), 6.97(d, J=9.2Hz, 1H), 4.11~4.06(m, 2H), 3.75(t, J=5.0Hz, 4H), 2.76~2.72(m, 2H), 2.58~2.53(m, 6H), 2.49~2.43(m, 4H), 1.83~1.65(m, 8H), 1.33~1.30(m, 3H)

Mass, m/e: 445(M⁺), 157(base)

Example 7-3

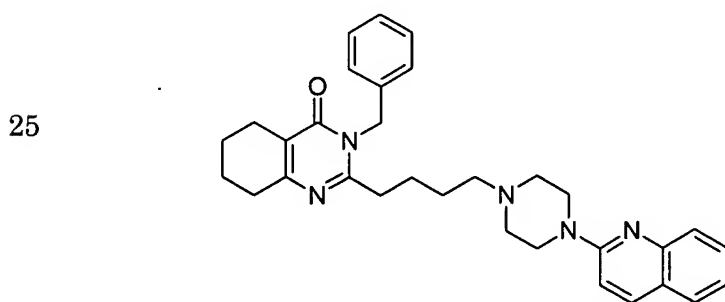


In the manner similar to Example 7-1,

10 3-propyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-5,6,7,8-tetrahydro-3H-quinazolin-4-one was synthesized.

¹H-NMR(CDCl₃)δ: 7.89(d, J=9.2Hz, 1H), 7.70(d, J=8.1Hz, 1H),
 7.59(dd, J=1.2Hz, 7.7Hz, 1H),
 15 7.53(ddd, J=1.5Hz, 6.9Hz, 8.5Hz, 1H),
 7.22(ddd, J=1.2Hz, 6.9Hz, 8.2Hz, 1H), 6.98(d, J=9.2Hz, 1H),
 3.95(t, J=7.7Hz, 2H), 3.76(t, J=4.6Hz, 4H), 2.74(t, J=7.7Hz, 2H),
 2.59(t, J=4.6Hz, 4H), 2.56~2.53(m, 2H), 2.51~2.42(m, 4H),
 1.86~1.58(m, 11H)
 20 Mass, m/e: 459(M⁺), 157(base)

Example 7-4



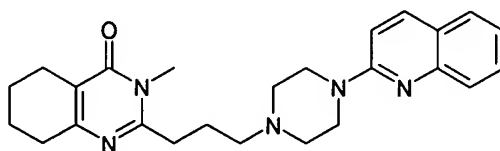
In the manner similar to Example 7-1,

30 3-benzyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-5,6,7,8-tetrahydro-3H-quinazolin-4-one was synthesized.

¹H-NMR(CDCl₃)δ: 7.23~7.20(m, 1H), 6.97(d, J=9.2Hz, 1H),
 7.87(d, J=8.9Hz, 1H), 7.69(d, J=8.9Hz, 1H),
 35 7.58(dd, J=8.1Hz, 1.2Hz, 1H), 7.57~7.50(m, 1H), 7.33~7.27(m, 3H),

7.23~7.19(m,1H),7.15(d,J=6.9Hz,2H),6.96(d,J=8.9Hz,1H),
 5.31(s,2H),3.73~3.71(m,4H),2.60~2.54(m,2H),2.52~2.50(m,6H),
 2.33(t,J=7.3Hz,2H),1.82~1.66(m,6H),1.56~1.52(m,4H)
 Mass,m/e:507(M⁺),157(base)

5

Example 7-5

10

In the manner similar to Example 7-1,
 3-methyl-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propyl]-5,6,7,8-
 tetrahydro-3H-quinazolin-4-one was synthesized.

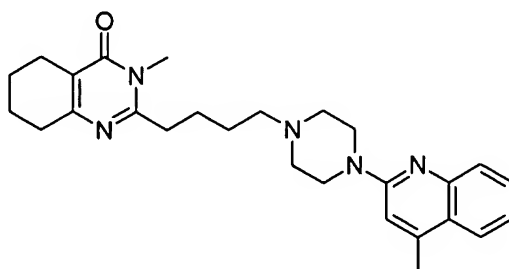
15

¹H-NMR(CDCl₃)δ:7.88(d,J=8.9Hz,1H),7.69(d,J=8.5Hz,1H),
 7.59(dd,J=1.1Hz,8.1Hz,1H),
 7.52(ddd,J=1.5Hz,6.9Hz,6.9Hz,1H),
 7.22(ddd,J=1.1Hz,6.9Hz,6.9Hz,1H),
 6.96(d,J=9.1Hz,1H),3.75~3.70(m,4H),3.55(s,3H),
 2.77(t,J=8.0Hz,2H),2.62~2.56(m,10H),1.99(q,J=7.3Hz,2H),
 1.81~1.68(m,4H)
 Mass,m/e:417(M⁺),240,178,157(base)

20

Example 7-6

25



30

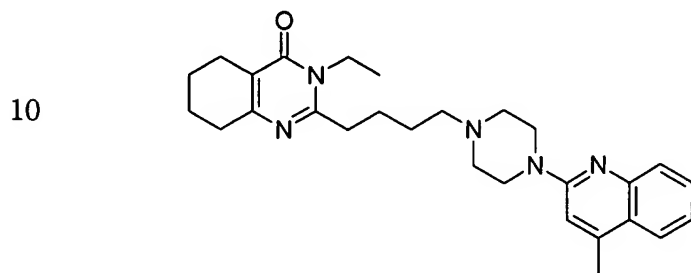
In the manner similar to Example 7-1,
 3-methyl-2-[4-[4-(4-methylquinolin-2-yl)piperazin-1-yl]butyl]-5,6,7,8-
 tetrahydro-3H-quinazolin-4-one was synthesized.

35

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.76(dd, $J=8.1\text{Hz}$, 1.2Hz, 1H),
 7.69(d, $J=8.5\text{Hz}$, 1H), 7.54~7.50(m, 1H), 7.25~7.22(m, 1H),
 6.83(s, 1H), 3.75(t, $J=5.0\text{Hz}$, 4H), 3.53(s, 3H), 2.74(t, $J=8.1\text{Hz}$, 2H),
 2.59~2.54(m, 9H), 2.50~2.43(m, 4H), 1.81~1.68(m, 8H)

5 Mass, m/e : 445(M^+), 171(base)

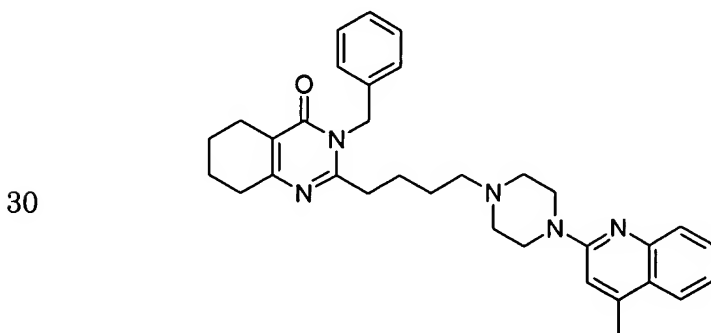
Example 7-7



In the manner similar to Example 7-1,
 15 3-ethyl-2-[4-[4-(4-methylquinolin-2-yl)piperazin-1-yl]butyl]-5,6,7,8-
 tetrahydro-3H-quinazolin-4-one was synthesized.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.76(d, $J=6.9\text{Hz}$, 1H), 7.69(d, $J=8.5\text{Hz}$, 1H),
 7.54~7.50(m, 1H), 7.26~7.22(m, 1H), 6.83(s, 1H), 4.12~4.05(m, 2H),
 20 3.77~3.74(m, 4H), 2.74(t, $J=7.7\text{Hz}$, 2H), 2.62~2.59(m, 4H),
 2.59(s, 3H), 2.56~2.53(m, 2H), 2.49~2.45(m, 4H), 1.83~1.67(m, 8H),
 1.33~1.29(m, 3H)
 Mass, m/e : 459(M^+), 171(base)

25 Example 7-8

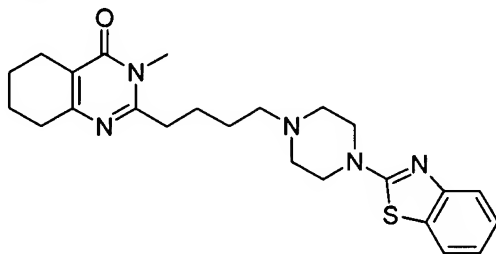


In the manner similar to Example 7-1,
 35 3-benzyl-2-[4-[4-(4-methylquinolin-2-yl)piperazin-1-yl]butyl]-5,6,7,8-

tetrahydro-3H-quinazolin-4-one was synthesized.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.76(dd, $J=8.1\text{Hz}, J=1.2\text{Hz}$, 1H),
 7.79(d, $J=7.7\text{Hz}$, 1H), 7.54~7.49(m, 1H), 7.33~7.21(m, 4H),
 7.16(s, 1H), 7.15(s, 1H), 6.81(s, 1H), 5.31(s, 2H), 3.72~3.70(m, 4H),
 2.67~2.64(m, 2H), 2.60~2.52(m, 2H), 2.59(s, 3H),
 2.50(t, $J=5.0\text{Hz}$, 4H), 2.34~2.30(m, 2H), 2.04~1.73(m, 4H),
 1.71~1.65(m, 2H), 1.58~1.50(m, 2H)
 Mass, m/e : 521(M^+), 171(base)

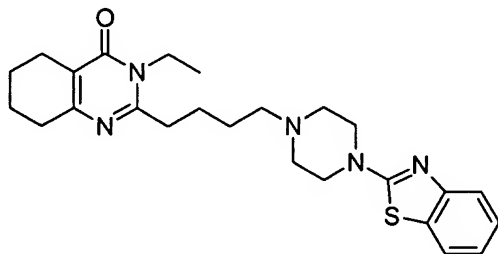
Example 7-9



In the manner similar to Example 7-1,
 2-[4-(4-benzothiazol-2-ylpiperazin-1-yl)butyl]-3-methyl-5,6,7,8-
 tetrahydro-3H-quinazolin-4-one was synthesized.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.59(d, $J=7.3\text{Hz}$, 1H), 7.54(d, $J=8.1\text{Hz}$, 1H),
 7.31~7.27(m, 1H), 7.09~7.05(m, 1H), 3.65~3.63(m, 4H), 3.52(s, 3H),
 2.75~2.71(m, 2H), 2.58~2.54(m, 6H), 2.50~2.43(m, 4H),
 1.81~1.63(m, 8H)
 Mass, m/e : 437(M^+), 96(base)

Example 7-10

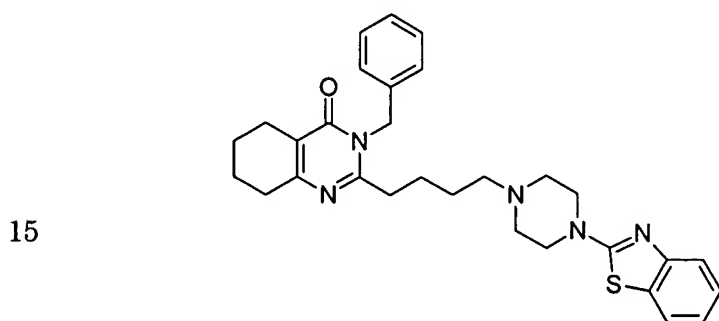


In the manner similar to Example 7-1,

2-[4-(4-benzothiazol-2-ylpiperazin-1-yl)butyl]-3-ethyl-5,6,7,8-tetrahydro-3H-quinazolin-4-one was synthesized.

¹H-NMR(CDCl₃)δ:7.61~7.54(m,2H),7.32~7.28(m,1H),
 7.10~7.06(m,1H),3.66~3.63(m,4H),3.31~3.24(m,2H),
 2.73~2.71(m,2H),2.59(t,J=5.0Hz,4H),2.54~2.53(m,2H),
 2.47~2.44(m,4H),1.85~1.65(m,8H),1.12(t,J=7.3Hz,3H)
 Mass,m/e:451(M⁺),96(base)

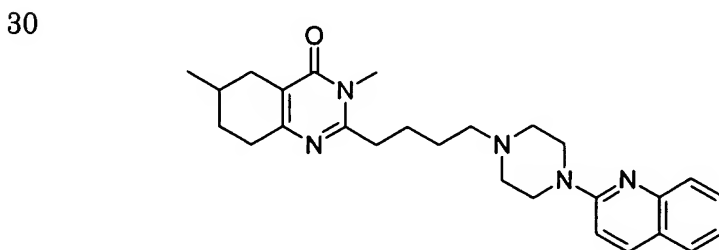
Example 7-11



In the manner similar to Example 7-1,
 2-[4-(4-benzothiazol-2-ylpiperazin-1-yl)butyl]-3-benzyl-5,6,7,8-tetrahydro-3H-quinazolin-4-one was synthesized.

¹H-NMR(CDCl₃)δ:7.59(d,J=6.9Hz,1H),7.54(d,7.3Hz,1H),
 7.33~7.27(m,6H),7.09~7.05(m,1H),4.43(d,J=5.8Hz,2H),
 3.61~3.59(m,4H),2.65(t,J=7.7Hz,2H),2.58(t,J=5.8Hz,2H),
 2.55~2.52(m,2H),2.51~2.48(m,4H),2.32(t,J=7.3Hz,2H),
 1.81~1.64(m,6H),1.55~1.49(m,2H)
 Mass,m/e:513(M⁺),91(base)

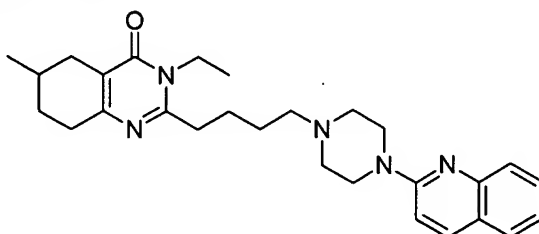
Example 7-12



Using 5-methyl-2-oxo-cyclohexanecarboxylic acid ethyl ester (a compound disclosed in J. Am. Chem. Soc., 85, 207-222 (1963)) as the starting material, 3,6-dimethyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-5,6,7,8-tetrahydro-3H-quinazolin-4-one was synthesized in the manner similar to Example 7-1.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.88(d, J=8.9Hz, 1H), 7.69(d, J=8.5Hz, 1H),
7.58(d, J=7.7Hz, 1H), 7.54~7.50(m, 1H), 7.23~7.19(m, 1H),
6.97(d, J=9.2Hz, 1H), 3.75(t, J=5.0Hz, 4H), 3.53(s, 3H),
2.74~2.68(m, 3H), 2.60~2.56(m, 7H), 2.45(t, J=7.3Hz, 2H),
2.03~1.96(m, 1H), 1.88~1.76(m, 3H), 1.71~1.65(m, 2H),
1.40~1.34(m, 1H), 1.06(d, J=6.6Hz, 3H)
Mass, m/e: 445(M^+), 157(base)

Example 7-13



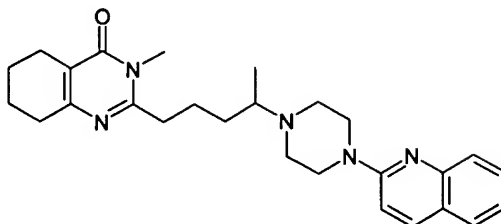
In the manner similar to Example 7-12, 3-ethyl-6-methyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-5,6,7,8-tetrahydro-3H-quinazolin-4-one was synthesized.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.88(d, J=9.0Hz, 1H), 7.69(d, J=8.5Hz, 1H),
7.58(dd, J=7.7Hz, 1.2Hz, 1H),
7.52(ddd, J=8.5Hz, 6.9Hz, 1.5Hz, 1H),
7.21(ddd, J=8.1Hz, 6.9Hz, 1.2Hz, 1H), 6.97(d, J=9.2Hz, 1H),
4.08(q, J=7.3Hz, 2H), 3.75(t, J=5.0Hz, 4H), 2.76~2.67(m, 3H),
2.60~2.56(m, 7H), 2.44(t, J=7.3Hz, 2H),
1.99(dd, J=17.3Hz, 10.0Hz, 1H), 1.87~1.72(m, 3H),
1.71~1.65(m, 2H), 1.39~1.35(m, 1H), 1.31(t, J=6.9Hz, 3H),
1.06(d, J=6.7Hz, 3H)

Mass, m/e: 459(M⁺), 157(base)

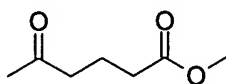
Example 7-14

5



Step 7-14-A: Synthesis of 5-oxo-hexanoic acid methyl ester

10



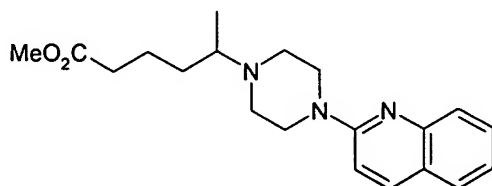
To a mixture of 30 ml of 4N aqueous sodium hydroxide and 30 ml of diethyl ether, 2.06 g of N-methyl-N-nitroso-urea was added consuming 20 minutes under cooling with ice, followed by 20 minutes' stirring. The diethyl ether layer was separated, into which 1.30 g of 5-oxo-hexanoic acid was added and stirred at room temperature for 2 hours. The solution was washed with saturated aqueous sodium hydrogencarbonate solution, dried over anhydrous magnesium sulfate and the solvent was concentrated under reduced pressure. The residue was purified on silica gel column chromatography (ethyl acetate : n-hexane = 1:3) to provide 1.15 g (80%) of 5-oxo-hexanoic acid methyl ester.

25

¹H-NMR(CDCl₃) δ: 3.66(s, 3H), 2.49(t, J=7.3Hz, 2H),
2.33(t, J=7.3Hz, 2H), 2.13(s, 3H), 1.89~1.84(m, 2H)
Mass, m/e: 145, 59(base)

Step 7-14-B: Synthesis of methyl 5-(4-quinolin-2-piperazin-1-yl)hexanoate

30



35

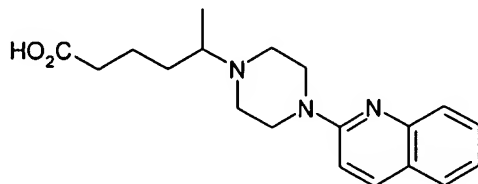
A mixture of 1.10 g of methyl 5-oxo-hexanoate as synthesized in above step 7-14-A, 1.36 g of 2-piperazin-1-ylquinoline, 20 mg of p-toluenesulfonic acid and 50 ml of toluene was heated under reflux for 16 hours, and the formed water was azeotropically removed. The solvent was concentrated under reduced pressure. The residue was dissolved in 50 ml of tetrahydrofuran, and the solution was stirred at room temperature for an hour while hydrogen chloride gas was introduced thereinto. Then 380 mg of sodium cyanotrihydroborate as dissolved in 10 ml of methanol was added, followed by 2 hours' stirring. To the solution, 0.1N aqueous potassium hydroxide was added, followed by extraction with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and the solvent was concentrated under reduced pressure. The residue was purified on silica gel column chromatography (ethyl acetate : n-hexane = 1:1) to provide 977 mg (45%) of methyl 5-(4-quinoline-2-ylpiperazin-1-yl)hexanoate.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.86(d, J=9.3Hz, 1H), 7.68(d, J=8.1Hz, 1H), 7.57(d, J=8.1Hz, 1H), 7.51(ddd, J=1.5Hz, 6.9Hz, 8.5Hz, 1H), 7.20(ddd, J=1.5Hz, 6.9Hz, 8.1Hz, 1H), 6.96(d, J=8.9Hz, 1H), 3.74~3.71(m, 4H), 3.67(s, 3H), 2.70~2.62(m, 3H), 2.60~2.55(m, 2H), 2.34(t, J=7.3Hz, 2H), 1.75~1.64(m, 4H), 1.00(d, J=6.6Hz, 3H)
Mass, m/e: 341(M^+), 157(base)

25

Step 7-14-C: Synthesis of 5-(4-quinoline-2-ylpiperazin-1-yl)hexanoic acid

30



To 10 ml of 1N sodium hydroxide : ethanol = 1:1 solution, 850 mg of methyl 5-(4-quinolin-2-ylpiperazin-1-yl)hexanoate as synthesized in above Step 7-14-B was added and heated under reflux

35

for an hour. Cooling the system, 2N hydrochloric acid was added to make the pH7, and the precipitate was recovered by filtration and dried to provide 728 mg (89%) of

5-(4-quinoline-2-ylpiperazin-1-yl)hexanoic acid.

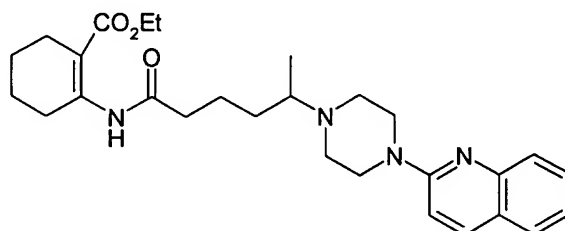
5

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.91(d, J=9.3Hz, 1H), 7.70(d, J=8.5Hz, 1H),
7.60(d, J=8.1Hz, 1H), 7.54(ddd, J=1.5Hz, 6.9Hz, 8.5Hz, 1H),
7.27~7.23(m, 1H), 6.95(d, J=9.2Hz, 1H), 4.05~3.95(m, 4H),
3.06~3.00(m, 3H), 2.98~2.94(m, 2H), 2.34(t, J=7.3Hz, 2H),
1.98~1.93(m, 1H), 1.75~1.64(m, 2H), 1.54~1.49(m, 1H),
1.16(d, J=6.9Hz, 3H)
Mass, m/e: 327(M^+), 157(base)

10

Step 7-14-D: Synthesis of ethyl 2-[5-(4-quinolin-2-ylpiperazin-1-yl)hexanoylamino]cyclohex-1-enecarboxylate

15



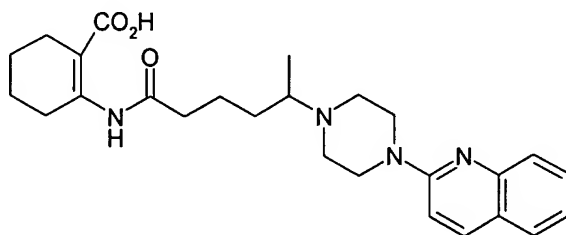
20

To a solution of 170 mg of ethyl 2-aminocyclohex-1-enecarboxylate as synthesized in Step 7-1-B in 5 ml of pyridine, 70 mg of phosphorus trichloride was added under cooling with ice, followed by 15 minutes' stirring. Raising the temperature to room temperature, 327 mg of 5-(4-quinoline-2-ylpiperazin-1-yl)hexanoic acid as synthesized in above Step 7-14-C was added to the solution and stirred for 3 hours. Distilling the pyridine off under reduced pressure, the residue was extracted with ethyl acetate and washed with water. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was concentrated under reduced pressure. The residue was purified on silica gel column chromatography (ethyl acetate) to provide 182 mg (38%) of ethyl 2-[5-(4-quinolin-2-ylpiperazin-1-yl)hexanoylamino]cyclohex-1-enecarboxylate.

35

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 11.61(br s, 1H), 7.86(d, $J=8.9\text{Hz}$, 1H),
 7.68(d, $J=8.5\text{Hz}$, 1H), 7.57(d, $J=7.7\text{Hz}$, 1H),
 7.51(ddd, $J=1.2\text{Hz}, 6.9\text{Hz}, 8.1\text{Hz}$, 1H), 7.22~7.18(m, 1H),
 6.96(d, $J=9.3\text{Hz}$, 1H), 4.14(q, $J=6.9\text{Hz}$, 2H), 3.80~3.70(m, 4H),
 2.98~2.95(m, 2H), 2.75~2.65(m, 3H), 2.64~2.56(m, 2H),
 2.34(t, $J=7.3\text{Hz}$, 2H), 2.31~2.28(m, 2H), 1.81~1.70(m, 2H),
 1.69~1.56(m, 6H), 1.26(t, $J=6.9\text{Hz}$, 3H), 1.01(d, $J=6.6\text{Hz}$, 3H)
 Mass, m/e : 478(M^+), 157(base)

Step 7-14-E: Synthesis of 2-[5-(4-quinolin-2-ylpiperazin-1-yl)hexanoylamino]-cyclohex-1-enecarboxylic acid



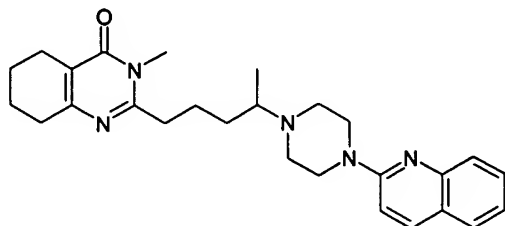
From ethyl 2-[5-(4-quinolin-2-ylpiperazin-1-yl)hexanoylamino]-cyclohex-1-enecarboxylate as synthesized in Step 7-14-D, 2-[5-(4-quinolin-2-ylpiperazin-1-yl)hexanoylamino]-cyclohex-1-enecarboxylic acid was synthesized in the manner similar to Step 7-1-E.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 12.32(br s, 1H), 7.91(d, $J=9.3\text{Hz}$, 1H),
 7.70(d, $J=8.5\text{Hz}$, 1H), 7.61(d, $J=8.1\text{Hz}$, 1H),
 7.55(ddd, $J=1.5\text{Hz}, 6.9\text{Hz}, 8.5\text{Hz}$, 1H), 7.28~7.23(m, 1H),
 6.95(d, $J=8.9\text{Hz}$, 1H), 4.05~3.97(m, 4H), 3.04~2.96(m, 3H),
 2.95~2.90(m, 2H), 2.43~2.26(m, 6H), 1.93~1.71(m, 2H),
 1.61~1.41(m, 6H), 1.19(d, $J=6.9\text{Hz}$, 3H)
 Mass, m/e : 406, 157(base)

Step 7-14-F: Synthesis of 3-methyl-2-[4-(4-quinolin-2-ylpiperazin-

1-yl)-pentyl][5,6,7,8-tetrahydro-3H-quinazolin-4-one

5



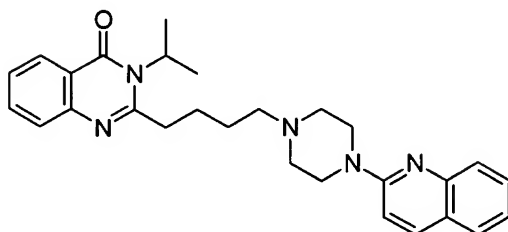
Using the 2-[5-(4-quinolin-2-ylpiperazin-1-yl)hexanoylamino]-cyclohex-1-enecarboxylic acid as synthesized in above Step 7-14-E, 3-methyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)pentyl]-5,6,7,8-tetrahydro-3H-quinazolin-4-one was synthesized in the manner similar to Step 7-1-F.

15

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.87(d, $J=8.9\text{Hz}$, 1H), 7.69(d, $J=8.5\text{Hz}$, 1H), 7.58(d, $J=8.1\text{Hz}$, 1H), 7.52(ddd, $J=1.5\text{Hz}$, 6.9Hz, 8.5Hz, 1H), 7.23~7.19(m, 1H), 6.96(d, $J=9.2\text{Hz}$, 1H), 3.77~3.71(m, 4H), 3.54(s, 3H), 2.74~2.68(m, 5H), 2.59~2.54(m, 4H), 2.50~2.47(m, 2H), 1.83~1.68(m, 8H), 1.01(d, $J=6.6\text{Hz}$, 3H)
Mass, m/e : 445, 157(base)

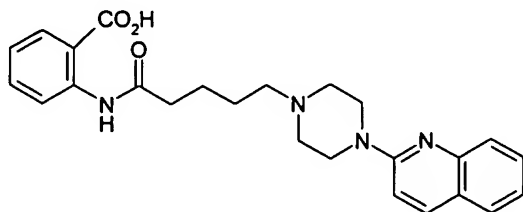
20 Example 7-15

25



Step 7-15-A: Synthesis of 2-[4-(4-quinolin-2-ylpiperazin-1-yl)-pentanoylamino]benzoic acid

30



35

Using ethyl anthranilate as the starting material,

2-[4-(4-quinolin-2-ylpiperazin-1-yl)pentanoylamino]benzoic acid was synthesized in the manner similar to Steps 7-1-C to 7-1-E.

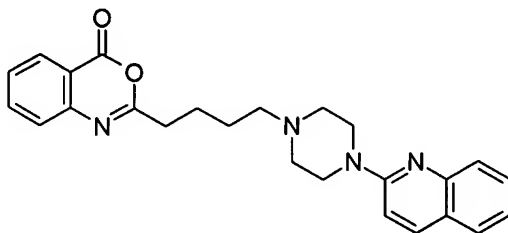
Because the product was difficultly soluble, no ^1H -NMR was taken.

5

Mass, m/e: 432(M^+), 414, 157(base)

Step 7-15-B: Synthesis of 2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3,1-benzoxazin-4-one

10



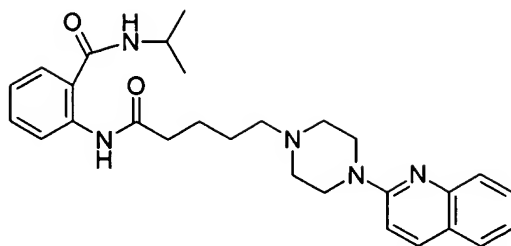
15

A mixture of 4.32 g of 2-[4-(4-quinolin-2-ylpiperazin-1-yl)pentanoylamino]benzoic acid as synthesized in above Step 7-15-A and 3.06 g of acetic anhydride was stirred at 80°C for an hour, and the solvent was distilled off under reduced pressure to provide 4.17 g (100%) of 2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3,1-benzoxazin-4-one.

^1H -NMR(CDCl_3) δ : 8.19(dd, $J=1.5\text{Hz}, 8.1\text{Hz}, 1\text{H}$),
 25 7.87(d, $J=9.3\text{Hz}, 1\text{H}$), 7.79(ddd, $J=1.5\text{Hz}, 6.9\text{Hz}, 8.5\text{Hz}, 1\text{H}$),
 7.69(d, $J=8.1\text{Hz}, 1\text{H}$), 7.61~7.54(m, 2H), 7.55~7.48(m, 2H),
 7.21(ddd, $J=1.2\text{Hz}, 6.9\text{Hz}, 8.1\text{Hz}, 1\text{H}$), 6.97(d, $J=9.2\text{Hz}, 1\text{H}$),
 3.75(t, $J=5.0\text{Hz}, 4\text{H}$), 2.74(t, $J=7.7\text{Hz}, 2\text{H}$), 2.58(t, $J=5.0\text{Hz}, 4\text{H}$),
 2.46(t, $J=7.3\text{Hz}, 2\text{H}$), 1.90(q, $J=7.7\text{Hz}, 2\text{H}$), 1.74~1.65(m, 2H)
 30 Mass, m/e: 414(M^+), 157(base)

Step 7-15-C: Synthesis of N-isopropyl-2-[5-(4-quinolin-2-ylpiperazin-1-yl)pentanoylamino]benzamide

35



5

In a glass tube, 414 mg of 2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3,1-benzoxazin-4-one as synthesized in above Step 7-15-B, 590 mg of isopropylamine and 5 ml of tetrahydrofuran were hermetically sealed and stirred for an hour at the exterior temperature of 80°C. Cooling the reaction mixture, the solvent was distilled off under reduced pressure, and the resulting residue was purified on silica gel column chromatography (dichloromethane : methanol = 10:1) to provide 275 mg (58%) of N-isopropyl-2-[5-(4-quinolin-2-ylpiperazin-1-yl)pentanoylamino]benzamide.

15

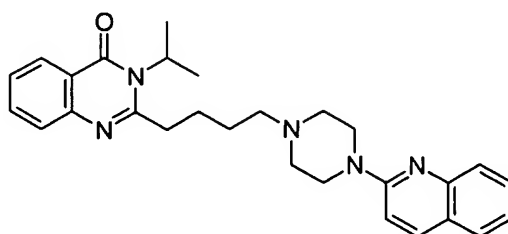
¹H-NMR(CDCl₃) δ: 11.11(br s, 1H), 8.61(dd, J=0.8Hz, 8.5Hz, 1H), 7.87(d, J=9.3Hz, 1H), 7.68(d, J=8.5Hz, 1H), 7.58(dd, J=1.2Hz, 8.1Hz, 1H), 7.51(ddd, J=1.2Hz, 6.9Hz, 8.1Hz, 1H), 7.45(ddd, J=1.5Hz, 6.9Hz, 8.9Hz, 1H), 7.41(dd, J=1.5Hz, 8.1Hz, 1H), 7.20(ddd, J=1.2Hz, 6.9Hz, 8.1Hz, 1H), 7.05(ddd, J=1.2Hz, 7.3Hz, 8.5Hz, 1H), 6.96(d, J=9.3Hz, 1H), 5.99~5.97(m, 1H), 4.26~4.21(m, 1H), 3.74(t, J=5.0Hz, 4H), 2.61~2.57(m, 4H), 2.45(t, J=7.3Hz, 2H), 1.81~1.75(m, 2H), 1.69~1.59(m, 2H), 1.26(d, J=6.6Hz, 6H)
Mass, m/e: 473(M⁺), 157(base)

20

25

Step 7-15-D: Synthesis of 3-isopropyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3H-quinazolin-4-one

30

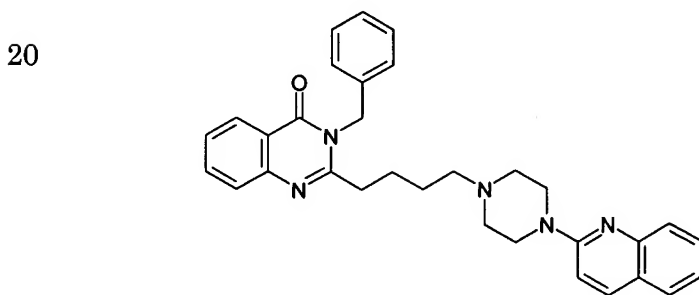


35

At 250°C, 200 mg of N-isopropyl-2-[5-(4-quinolin-2-ylpiperazin-1-yl)pentanonylamino]benzamide as synthesized in above Step 7-15-C was stirred for an hour. Cooling the system, the residue was purified on silica gel column chromatography (dichloromethane : methanol =15:1) to provide 25 mg (13%) of 3-isopropyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3H-quinazolin-4-one.

¹H-NMR(CDCl₃)δ:8.21(dd,J=1.2Hz,8.1Hz,1H),
 7.88(d,J=9.3Hz,1H),7.70~7.66(m,2H),7.64~7.62(m,1H),
 7.60~7.57(m,2H),7.52(ddd,J=1.5Hz,6.9Hz,8.5Hz,1H),
 7.40(ddd,J=1.2Hz,6.9Hz,8.1Hz,1H),7.24~7.19(m,1H),
 6.97(d,J=9.3Hz,1H),4.64~4.56(m,1H),3.78~3.74(m,4H),
 2.90(t,J=7.7Hz,2H),2.61~2.57(m,4H),2.50(t,J=7.7Hz,2H),
 1.93~1.85(m,2H),1.79~1.69(m,2H),1.68(d,J=6.6Hz,6H)
 Mass,m/e:455(M⁺),157(base)

Example 7-16

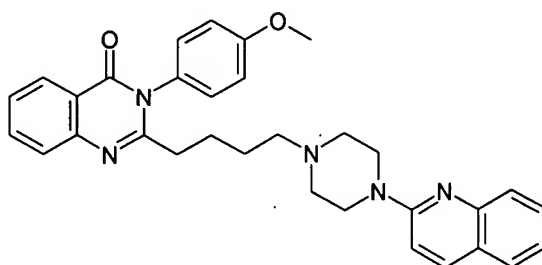


A mixture of 207 mg of 2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3,1-benzoxazin-4-one as synthesized in above Step 7-15-B and 150 mg of benzylamine was stirred at 250°C for an hour. Cooling the solution, the residue was purified on silica gel column chromatography (dichloromethane : methanol = 15:1) to provide 163 mg (65%) of 3-benzyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3H-quinazolin-4-one.

¹H-NMR(CDCl₃)δ:8.30(dd,J=1.2Hz,8.1Hz,1H),
 7.88(d,J=8.9Hz,1H),7.74(ddd,J=1.2Hz,6.9Hz,8.5Hz,1H),

7.72~7.57(m,2H),7.53(dd,J=1.1Hz,6.9Hz,1H),
 7.35~7.16(m,7H),7.46(ddd,J=1.2Hz,6.9Hz,8.1Hz,1H),
 6.96(d,J=8.9Hz,1H),5.43(s,3H),3.74~3.70(m,4H),
 2.79(t,J=7.7Hz,2H),2.54~2.50(m,4H),2.38(t,J=7.3Hz,2H),
 1.86~1.79(m,2H),1.63~1.55(m,2H)
 Mass,m/e:503(M⁺),157(base),91

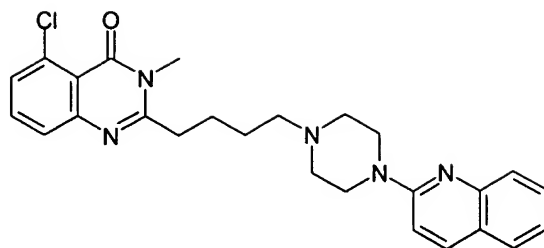
Example 7-17



In the manner similar to Example 7-16,
 3-(4-methoxyphenyl)-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3H-
 quinazolin-4-one was synthesized.

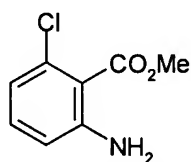
¹H-NMR(CDCl₃)δ:8.26(dd,J=1.5Hz,8.1Hz,1H),
 7.87(d,J=9.2Hz,1H),7.78~7.76(m,1H),7.73(d,J=1.5Hz,1H),
 7.69(d,J=8.1Hz,1H),7.58(d,J=8.1Hz,1H),
 7.52(ddd,J=1.2Hz,6.9Hz,8.1Hz,1H),
 7.45(ddd,J=1.2Hz,6.9Hz,8.1Hz,1H),
 7.23~7.19(m,1H),7.16(dd,J=2.3Hz,6.5Hz,2H),
 7.05(dd,J=2.3Hz,6.5Hz,2H),6.96(d,J=9.2Hz,1H),3.86(s,3H),
 3.72~3.70(m,4H),2.52~2.48(m,6H),2.32(t,J=7.3Hz,2H),
 1.80~1.71(m,2H),1.53~1.49(m,2H)
 Mass,m/e:519(M⁺),307,157(base)

Example 7-18



5

Step 7-18-A: Synthesis of methyl 2-amino-6-chlorobenzoate



10

To a mixture of 20 ml of 4N sodium hydroxide and 50 ml of diethyl ether, 2.7 g of N-methyl-N-nitrosourea was added under cooling with ice and stirred for 30 minutes. The organic layer was separated and added to a solution of 915 mg of 2-amino-6-chlorobenzoic acid in 20 ml of diethyl ether, followed by an hour's stirring at room temperature. The solution was washed with saturated aqueous sodium hydrogencarbonate solution, dried over anhydrous magnesium sulfate and the solvent was distilled off under reduced pressure. The residue was purified on silica gel column chromatography (n-hexane : ethyl acetate = 3:1) to provide 790 mg (80%) of methyl 2-amino-6-chlorobenzoate.

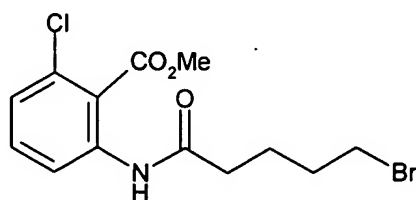
20

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.07(t, $J=8.1\text{Hz}$, 1H),
 6.74(dd, $J=0.8\text{Hz}$, 7.7Hz, 1H), 6.57(dd, $J=0.8\text{Hz}$, 8.1Hz, 1H),
 4.86(br s, 2H), 3.93(s, 3H)
 Mass, m/e : 185(M^+), 153(base), 126, 90

25

Step 7-18-B: Synthesis of methyl 2-(5-bromopentanoylamino)-6-chlorobenzoate

30

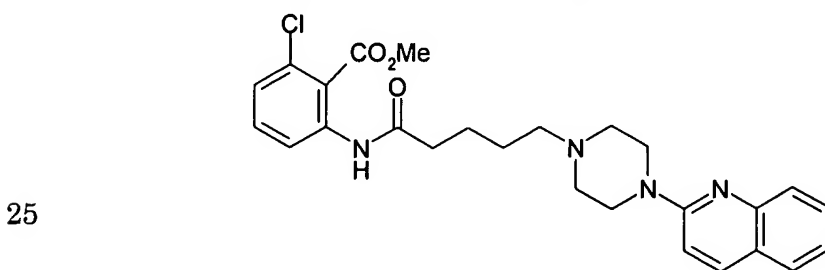


35

To a solution of 750 mg of methyl 2-amino-6-chlorobenzoate as synthesized in above Step 7-18-A in 10 ml of tetrahydrofuran, first 700 mg of pyridine and then 800 mg of 5-bromovaleryl chloride were added under cooling with ice. The solution was warmed to room temperature, stirred for an hour and the solvent was distilled off under reduced pressure. The residue was extracted with ethyl acetate, washed with saturated aqueous sodium hydrogencarbonate solution, 1N hydrochloric acid and saturated brine, dried over anhydrous magnesium sulfate and the solvent was distilled off under reduced pressure to provide 1.34 g (96%) of methyl 2-(5-bromopentanoylamino)-6-chlorobenzoate.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 9.07(br s, 1H), 8.27(d, $J=8.1\text{Hz}$, 1H), 7.35(t, $J=8.1\text{Hz}$, 1H), 7.17(dd, $J=0.8\text{Hz}$, 8.1Hz , 1H), 3.98(s, 3H), 3.44(t, $J=6.6\text{Hz}$, 4H), 2.41(t, $J=7.3\text{Hz}$, 2H), 1.99~1.91(m, 2H), 1.90~1.83(m, 2H)
Mass, m/e : 347(M^+), 185, 55(base)

Step 7-18-C: Synthesis of methyl 2-chloro-6-[5-(4-quinolin-2-ylpiperazin-1-yl)pentanoylamino]benzoate

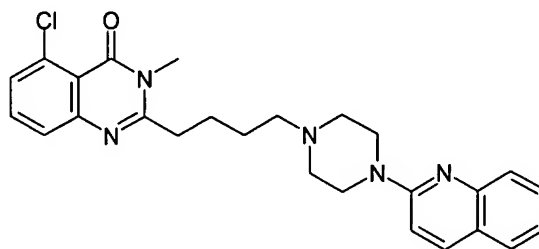


A mixture of 1.29 g of methyl 2-(5-bromopentanoylamino)-6-chloro-benzoate as synthesized in above Step 7-18-B, 800 mg of 2-piperazin-1-ylquinoline as synthesized in Step 7-1-A, 400 mg of triethylamine and 20 ml of toluene was heated under reflux for 3 hours. After cooling, the solution was washed with water, dried over anhydrous magnesium sulfate and the solvent was distilled off under reduced pressure. The residue was purified on silica gel column chromatography (ethyl acetate : methanol =15:1) to provide 1.13 g (64%) of methyl 2-chloro-6-[5-(4-quinolin-2-ylpiperazin-1-

yl)pentanoylamino]benzoate.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 9.08(br s, 1H), 8.28(d, $J=8.5\text{Hz}$, 1H),
 7.87(d, $J=8.9\text{Hz}$, 1H), 7.69(d, $J=8.1\text{Hz}$, 1H), 7.58(d, $J=6.5\text{Hz}$, 1H),
 5 7.56(d, $J=8.3\text{Hz}$, 1H), 7.52(ddd, $J=1.5\text{Hz}$, 6.9Hz, 8.5Hz, 1H),
 7.35(t, $J=8.5\text{Hz}$, 1H), 7.23~7.15(m, 2H), 6.97(d, $J=9.2\text{Hz}$, 1H),
 3.97(s, 3H), 3.74(t, $J=5.0\text{Hz}$, 4H), 2.57(t, $J=5.0\text{Hz}$, 4H),
 2.45~2.40(m, 4H), 1.81~1.73(m, 2H), 1.66~1.59(m, 2H)
 Mass, m/e : 480(M^+), 157(base)

Step 7-18-D: Synthesis of 5-chloro-3-methyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3H-quinazolin-4-one



20 A mixture of 250 mg of methyl 2-chloro-6-[5-(4-quinolin-2-ylpiperazin-1-yl)pentanoylamino]benzoate as synthesized in the above Step 7-18-C and 5 ml of 40% methylamine in methanol solution was hermetically sealed in a glass tube and stirred for 18 hours at the exterior temperature of 100°C. After cooling, the
 25 solvent was distilled off from the solution, and the residue was purified on silica gel column chromatography (dichloro methane : methanol = 15:1) to provide 96 mg (40%) of
 5-chloro-3-methyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3H-quinazolin-4-one.

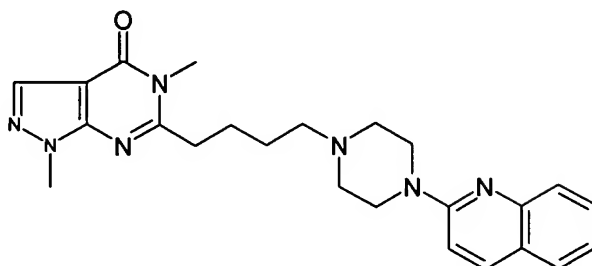
30 $^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.88(d, $J=8.9\text{Hz}$, 1H), 7.70(d, $J=8.5\text{Hz}$, 1H),
 7.59(dd, $J=1.2\text{Hz}$, 8.1Hz, 1H), 7.56~7.50(m, 3H),
 7.43(d, $J=2.3\text{Hz}$, 1H), 7.22(ddd, $J=1.2\text{Hz}$, 6.9Hz, 8.1Hz, 1H),
 6.97(d, $J=9.2\text{Hz}$, 1H), 3.76(t, $J=5.0\text{Hz}$, 4H), 3.59(s, 3H),
 35 2.85(t, $J=7.7\text{Hz}$, 2H), 2.59(t, $J=5.0\text{Hz}$, 4H), 2.49(t, $J=7.3\text{Hz}$, 2H),

1.95~1.86(m,2H),1.75~1.68(m,2H)

Mass,m/e:461(M⁺),157(base)

Example 7-19

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10

Using ethyl 5-amino-1-methyl-1H-pyrazole-4-carboxylate as the starting material, 1,5-dimethyl-6-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-1,5-dihydropyrazolo[3,4-d]pyrimidin-4-one was synthesized in the manner similar to Example 7-18.

15

¹H-NMR(CDCl₃)δ:8.01(s,1H),7.89(d,J=8.9Hz,1H),

7.70(d,J=8.5Hz,1H),7.62~7.58(m,1H),

7.54(ddd,J=1.5Hz,6.9Hz,8.5Hz,1H),

20

7.23(ddd,J=1.2Hz,6.9Hz,8.1Hz,1H),6.98(d,J=8.9Hz,1H),

3.77(t,J=5.0Hz,4H),3.61(s,3H),3.59(s,3H),2.86(t,J=7.3Hz,2H),

2.60(t,J=4.6Hz,4H),2.50(t,J=7.3Hz,2H),1.94~1.86(m,2H),

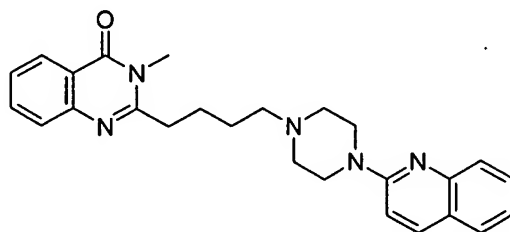
1.75~1.70(m,2H)

Mass,m/e:431(M⁺),157(base)

25

Example 7-20

30

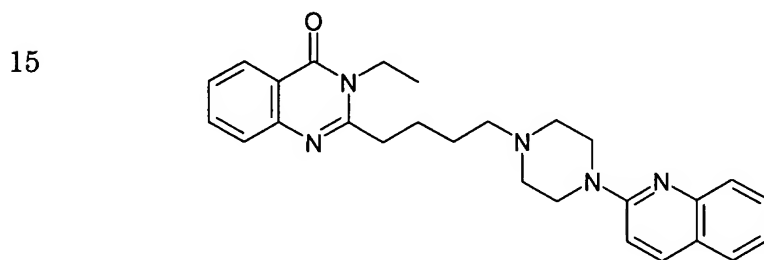


Using ethyl anthranilate as the starting material, 3-methyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3H-quinazolin-4-one was synthesized in the manner similar to Example 7-18.

35

¹H-NMR(CDCl₃)δ:8.26(dd,J=1.2Hz,8.1Hz,1H),
 7.89(d,J=9.3Hz,1H),7.72(ddd,J=1.5Hz,6.9Hz,8.5Hz,1H),
 7.71~7.69(m,1H),7.64~7.62(m,1H),7.62~7.58(m,1H),
 5 7.53(ddd,J=1.5Hz,6.9Hz,8.5Hz,1H),
 7.44(ddd,J=1.2Hz,6.9Hz,8.1Hz,1H),
 7.22(ddd,J=1.2Hz,6.9Hz,8.1Hz,1H),6.98(d,J=9.2Hz,1H),
 3.76(t,J=5.1Hz,4H),3.64(s,3H),2.89(t,J=8.1Hz,2H),
 2.59(t,J=5.0Hz,4H),2.49(t,J=7.3Hz,2H),1.93(q,J=7.7Hz,2H),
 10 1.79~1.70(m,2H)
 Mass,m/e:427(M⁺),157(base)

Example 7-21

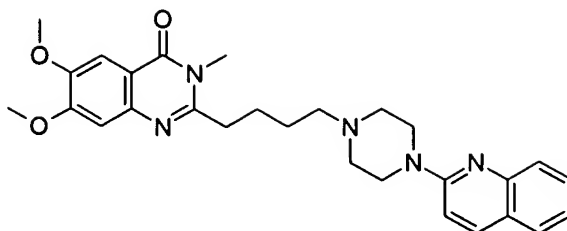


20 Using ethyl anthranilate as the starting material,
 3-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3H-quinazolin-4-one was
 synthesized in the manner similar to Example 7-18.

H-NMR(CDCl₃)δ:8.25(dd,J=1.5Hz,8.1Hz,1H),
 25 7.89(d,J=9.2Hz,1H),7.71(ddd,J=1.5Hz,6.9Hz,8.5Hz,1H),
 7.70(dd,J=1.2Hz,8.5Hz,1H),7.64~7.58(m,2H),
 7.53(ddd,J=1.5Hz,6.9Hz,8.5Hz,1H),
 7.43(ddd,J=1.5Hz,6.9Hz,8.5Hz,1H),
 7.22(ddd,J=1.2Hz,6.9Hz,8.1Hz,1H),6.98(d,J=8.9Hz,1H),
 30 4.19(q,J=6.9Hz,3H),3.77(t,J=5.0Hz,4H),2.88(t,J=7.7Hz,2H),
 2.60(t,J=5.0Hz,4H),2.50(t,J=7.3Hz,2H),1.95(q,J=7.7Hz,2H),
 1.80~1.70(m,2H),1.37(t,J=6.9Hz,3H)
 Mass,m/e:441(M⁺),157(base)

35 Example 7-22

5

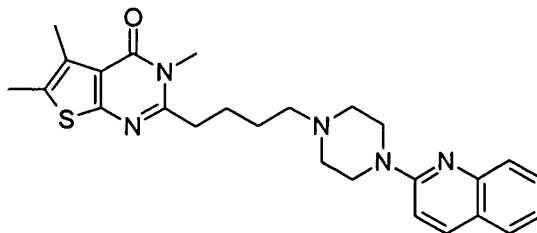


Using 2-amino-4,5-dimethoxybenzoic acid as the starting material, 6,7-dimethoxy-3-methyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3H-quinazolin-4-one was synthesized in the manner similar to Example 7-18.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.88(d, $J=8.9\text{Hz}$, 1H), 7.69(d, $J=8.5\text{Hz}$, 1H), 7.58(dd, $J=1.2\text{Hz}$, 8.1Hz, 1H), 7.57(s, 1H), 7.53(ddd, $J=1.5\text{Hz}$, 6.9Hz, 8.5Hz, 1H), 7.22(ddd, $J=1.2\text{Hz}$, 6.9Hz, 8.1Hz, 1H), 7.03(s, 1H), 6.97(d, $J=9.2\text{Hz}$, 1H), 3.99(s, 3H), 3.98(s, 3H), 3.76(t, $J=5.0\text{Hz}$, 4H), 3.64(s, 3H), 2.86(t, $J=7.3\text{Hz}$, 2H), 2.59(t, $J=5.0\text{Hz}$, 4H), 2.49(t, $J=7.3\text{Hz}$, 2H), 1.93~1.85(m, 2H), 1.75~1.56(m, 2H)
Mass, m/e : 487(M^+), 157(base)

Example 7-23

25



30

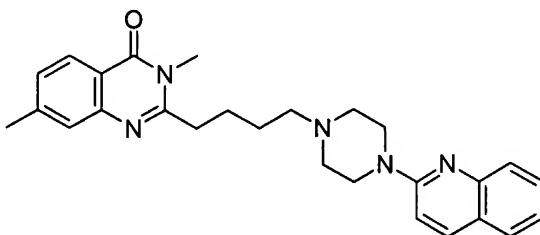
Using ethyl 2-amino-4,5-dimethylthiophene-3-carboxylate as the starting material, 3,5,6-trimethyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3H-thieno[2,3-d]pyrimidin-4-one was synthesized in the manner similar to Example 7-18.

35

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.88(d, $J=9.3\text{Hz}$, 1H), 7.69(d, $J=8.1\text{Hz}$, 1H),
 7.58(d, $J=8.1\text{Hz}$, 1H), 7.54~7.50(m, 1H), 7.23~7.19(m, 1H),
 6.97(d, $J=8.2\text{Hz}$, 1H), 3.76(t, $J=5.0\text{Hz}$, 4H), 3.58(s, 3H),
 2.83~2.79(m, 2H), 2.59(t, $J=5.0\text{Hz}$, 4H), 2.50~2.38(m, 2H),
 2.46(s, 3H), 2.36(s, 3H), 1.89~1.83(m, 2H), 1.73~1.68(m, 2H)
 Mass, m/e : 461(M^+), 157(base)

Example 7-24

10



15

Using ethyl 2-amino-4-methylbenzoate as the starting material, 3,7-dimethyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3H-quinazolin-4-one was synthesized in the manner similar to Example 7-18.

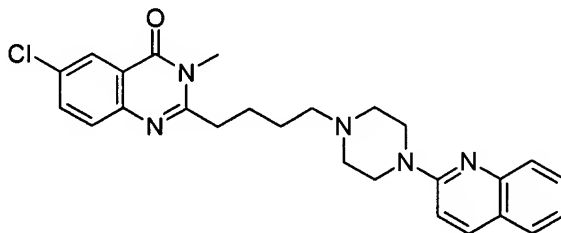
20

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.13(d, $J=8.1\text{Hz}$, 1H), 7.88(d, $J=8.9\text{Hz}$, 1H),
 7.69(d, $J=8.1\text{Hz}$, 1H), 7.59(d, $J=8.1\text{Hz}$, 1H), 7.54~7.50(m, 1H),
 7.42(s, 1H), 7.24~7.19(m, 2H), 6.97(d, $J=9.2\text{Hz}$, 1H),
 3.76~3.75(m, 4H), 3.63(s, 3H), 2.88~2.84(m, 2H),
 2.60~2.58(m, 4H), 2.51~2.48(m, 5H), 1.93~1.89(m, 2H),
 1.74~1.71(m, 2H)
 Mass, m/e : 441(M^+), 157(base)

25

Example 7-25

30



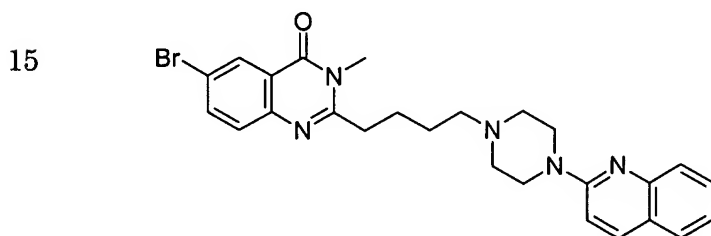
35

Using ethyl 2-amino-5-chlorobenzoate as the starting material,

6-chloro-3-methyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3H-quinazolin-4-one was synthesized in the manner similar to Example 7-18.

- 5 ¹H-NMR(CDCl₃)δ:8.21(d,J=2.3Hz,1H),7.89(d,J=8.9Hz,1H),
 7.69(d,J=8.5Hz,1H),7.65~7.62(m,1H),7.60~7.51(m,3H),
 7.24~7.20(m,1H),6.98(d,J=8.9Hz,1H),3.76(br s,4H),3.64(s,3H),
 2.87(t,J=7.7Hz,2H),2.59(br s,4H),2.51~2.47(m,2H),
 1.94~1.88(m,2H),1.75~1.71(m,2H)
 10 Mass,m/e:461(M⁺),157(base)

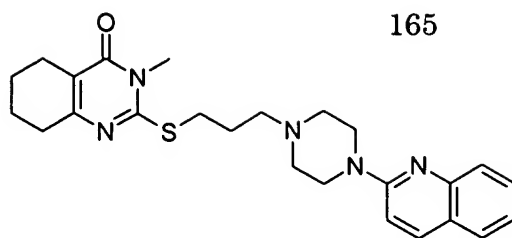
Example 7-26



- 20 Using ethyl 2-amino-5-bromobenzoate as the starting material,
 6-bromo-3-methyl-2-[4-(4-quinolin-2-ylpiperazin-1-yl)butyl]-3H-quinazolin-4-one was synthesized in the manner similar
 to Example 7-18.

- 25 ¹H-NMR(CDCl₃)δ:8.38(d,J=2.3Hz,1H),7.88(d,J=9.2Hz,1H),
 7.78(dd,J=8.5Hz,J=2.3Hz,1H),7.69(d,J=8.5Hz,1H),
 7.60~7.58(m,1H),7.55~7.49(m,2H),7.24~7.20(m,1H),
 6.97(d,J=9.2Hz,1H),3.76(t,J=5.0Hz,4H),3.63(s,3H),
 2.86(t,J=7.7Hz,2H),2.59(t,J=5.0Hz,4H),2.51~2.47(m,2H),
 30 1.97~1.87(m,2H),1.77~1.64(m,2H)
 Mass,m/e:505(M⁺),157(base)

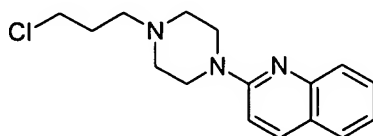
Example 7-27



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Step 7-27-A: Synthesis of 2-[4-(3-chloropropyl)piperazin-1-yl]quinoline

10



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In 5 ml of acetone, 853 mg of 2-piperazin-1-ylquinoline as synthesized in Step 7-1-A was dissolved and to which 160 mg of sodium hydroxide as dissolved in 5 ml of water was added. Into the mixed liquid 0.5 ml of 1-bromo-3-chloropropane was dropped, followed by stirring for an overnight at room temperature. After addition of diethyl ether, the organic layer was washed with saturated aqueous sodium hydrogencarbonate solution, and the organic layer was dried over anhydrous magnesium sulfate.

20

Distilling the solvent off under reduced pressure, the residue was purified on silica gel column chromatography (chloroform : methanol = 50:1) to provide 1.10 g (95%) of 2-[4-(3-chloropropyl)piperazin-1-yl]quinoline.

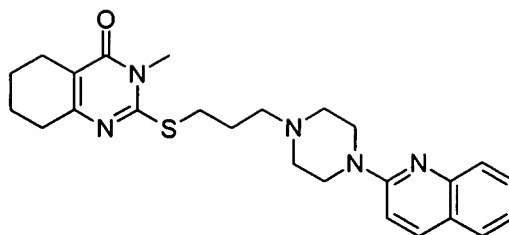
25

$^1\text{H-NMR}(\text{CDCl}_3)$: 7.89(d, $J=9.2\text{Hz}$, 1H), 7.70(d, $J=8.4\text{Hz}$, 1H), 7.59(dd, $J=1.4\text{Hz}$, 8.0Hz, 1H), 7.53(ddd, $J=1.5\text{Hz}$, 7.1Hz, 8.5Hz, 1H), 7.22(ddd, $J=1.1\text{Hz}$, 6.9Hz, 8.0Hz, 1H), 6.98(d, $J=9.2\text{Hz}$, 1H), 3.75(t, $J=5.1\text{Hz}$, 4H), 3.61(t, $J=6.5\text{Hz}$, 2H), 2.63~2.43(m, 6H), 2.04~1.97(m, 2H)
Mass, m/e : 289(M^+), 157(base)

30

Step 7-27-B: Synthesis of 3-methyl-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylthio]-5,6,7,8-tetrahydro-3H-quinazolin-4-one

35



5

A mixture of 234 mg of potassium 3-methyl-4-oxo-3,4,5,6,7,8-hexahydroquinazoline-2-thiolate (a compound shown in J. Med. Chem., 40, 574 – 585 (1997)), 290 mg of 2-[4-(3-chloropropyl)-piperazin-1-yl]quinoline as synthesized in above Step 7-27-A and 5 ml of 2-propanol was heated under reflux for an overnight. The residue was purified on silica gel column chromatography (chloroform : methanol = 10:1) to provide 467 mg (quantitative) of 3-methyl-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylthio]-5,6,7,8-tetrahydro-3H-quinazolin-4-one.

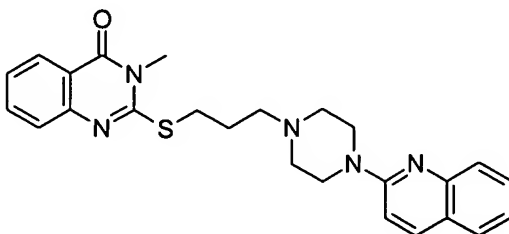
15

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.88(d, J=9.3Hz, 1H), 7.69(d, J=8.5Hz, 1H), 7.59(dd, J=8.1Hz, 1.2Hz, 1H), 7.55~7.51(m, 1H), 7.23~7.20(m, 1H), 6.97(d, J=9.3Hz, 1H), 3.76(t, J=5.0Hz, 4H), 3.48(s, 3H), 3.23(t, J=7.3Hz, 2H), 2.60(t, J=5.0Hz, 4H), 2.56~2.51(m, 4H), 2.49~2.46(m, 2H), 2.01~1.93(m, 2H), 1.78~1.70(m, 4H)
Mass, m/e: 449(M^+), 157(base)

20

Example 7-28

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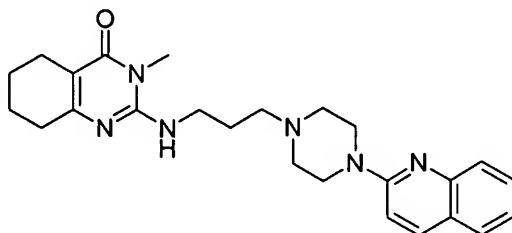
Using potassium 3-methyl-4-oxo-3,4-dihydroquinazoline-2-thiolate as the starting material, 3-methyl-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylthio]-3H-quinazolin-4-one was synthesized in the manner similar to Example 7-27.

35

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.21(dd, $J=8.1\text{Hz}, 1.5\text{Hz}, 1\text{H}$),
 7.88(d, $J=9.2\text{Hz}, 1\text{H}$), 7.71~7.66(m, 2H), 7.59(d, $J=7.7\text{Hz}, 1\text{H}$),
 7.55~7.51(m, 2H), 7.39~7.35(m, 1H), 7.24~7.20(m, 1H),
 6.98(d, $J=9.2\text{Hz}, 1\text{H}$), 3.79~3.77(m, 4H), 3.65(s, 3H),
 3.39~3.35(m, 2H), 2.64~2.57(m, 6H), 2.09~2.02(m, 2H)
 Mass, m/e : 445(M^+), 157(base)

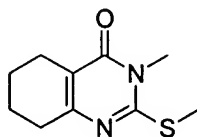
Example 7-29

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15 Step 7-29-A: Synthesis of 3-methyl-2-methylthio-5,6,7,8-tetrahydro-3H-quinazolin-4-one

20

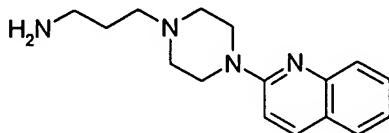


To a mixture of 10 ml of tetrahydrofuran and 5 ml of dimethylformamide, 340 mg of potassium 3-methyl-4-oxo-3,4,5,6,7,8-hexahydroquinazoline-2-thiolate was added, followed by addition of
 210 mg of methyl iodide and an overnight's stirring at room
 temperature. The solution was concentrated, to which chloroform
 was added, followed by washing with saturated brine and drying over
 anhydrous magnesium sulfate. Distilling the solvent off under
 reduced pressure, 310 mg (quantitative) of
 3-methyl-2-methylthio-5,6,7,8-tetrahydro-3H-quinazolin-4-one was
 obtained.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 3.49(s, 3H), 2.56~2.54(m, 2H), 2.54(s, 3H),
 2.49~2.46(m, 2H), 1.77~1.70(m, 4H)
 Mass, m/e : 210(M^+), 165(base)

Step 7-29-B: Synthesis of 2-[4-(3-aminopropyl)piperazin-1-yl]quinoline

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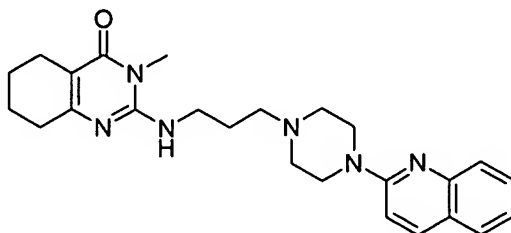
To 30 ml of ethanol, 1.52 g of 2-[3-(4-quinolin-2-ylpiperazin-1-yl)propyl]isoindol-1,3-dione (a compound shown in Pol. J. Chem., 75, 71-78 (2001)) was added, followed by addition of 1.50 g of hydrazine monohydrate as dissolved in 10 ml of ethanol and 7 hours' heating under reflux. After cooling the reaction system, insoluble matter was removed by filtration and the solvent was distilled off under reduced pressure. After being rendered to alkaline with 5N sodium hydroxide, the residue was extracted with chloroform, washed with saturated brine, dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure to provide 0.99 g (96%) of 2-[4-(3-aminopropyl)piperazin-1-yl]quinoline.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.87(d, J=8.9Hz, 1H), 7.69(d, J=8.5Hz, 1H), 7.58(d, J=8.1Hz, 1H), 7.52(ddd, J=1.5Hz, 6.9Hz, 8.5Hz, 1H), 7.23(ddd, J=1.2Hz, 6.9Hz, 8.1Hz, 1H), 6.97(d, J=8.9Hz, 1H), 3.75(t, J=5.4Hz, 4H), 2.78(t, J=6.9Hz, 2H), 2.58(t, J=5.4Hz, 4H), 2.46(t, J=7.3Hz, 2H), 1.78~1.63(m, 2H)

Mass, m/e: 270(M^+), 157(base)

Step 7-29-C: Synthesis of 3-methyl-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylamino]-5,6,7,8-tetrahydro-3H-quinazolin-4-one

30

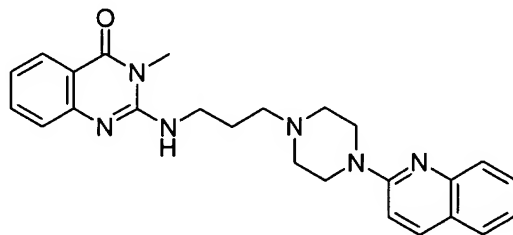


A mixture of 420 mg of 3-methyl-2-methylsulfanyl-5,6,7,8-

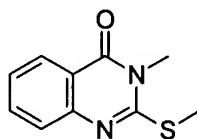
tetrahydro-3H-quinazolin-4-one as synthesized in Step 7-29-A and 540 mg of 2-[4-(3-aminopropyl)piperazin-1-yl]quinoline as synthesized in above Step 7-29-B was heated under stirring at 140°C for 6 hours. The residue was purified on silica gel column chromatography (chloroform : methanol = 10:1) to provide 420 mg (48%) of 3-methyl-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylamino]-5,6,7,8-tetrahydro-3H-quinazolin-4-one.

¹H-NMR(CDCl₃)δ:7.91(d,J=9.3Hz,1H),7.70(d,J=8.5Hz,1H),
7.60(d,J=8.1Hz,1H),7.54(ddd,J=8.5Hz,6.9Hz,1.5Hz,1H),
7.26~7.22(m,1H),6.98(d,J=8.9Hz,1H),6.69(br s,1H);
3.77(br s,4H),3.56~3.52(m,2H),3.48(s,3H),2.67(br s,4H),
2.64~2.61(m,2H),2.54(s,3H),2.49~2.40(m,4H),1.88~1.87(m,2H),
1.77~1.70(m,4H)
Mass,m/e:432(M⁺),157(base)

Example 7-30



Step 7-30-A: Synthesis of 3-methyl-2-methylsulfanyl-3H-quinazolin-4-one

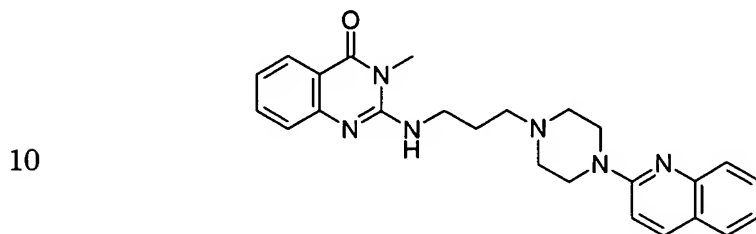


Using potassium 3-methyl-4-oxo-3,4-dihydroquinazoline-2-thiolate as the starting material, 3-methyl-2-methylsulfanyl-3H-quinazolin-4-one was synthesized in the manner similar to above Step 7-29-A.

¹H-NMR(CDCl₃)δ:8.22~8.20(m,1H),7.70~7.65(m,1H),

7.57~7.55(m,1H),7.36(ddd,J=8.1Hz,J=6.9Hz,J=1.2Hz,1H),
 3.61(s,3H),2.66(s,3H)
 Mass,m/e:206(M⁺),161(base)

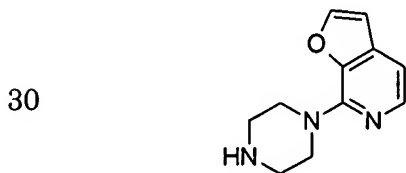
5 Step 7-30-B: Synthesis of 3-methyl-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylamino]-3H-quinazolin-4-one



Using 3-methyl-2-methylsulfanyl-3H-quinazolin-4-one as synthesized in above Step 7-30 A as the starting material, 3-methyl-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylamine]-3H-quinazolin-4-one
 15 was synthesized in the manner similar to Step 7-29-B.

¹H-NMR(CDCl₃)δ:8.10(dd,J=8.1Hz,1.2Hz,1H),
 7.92(d,J=9.2Hz,1H),7.72(d,J=8.5Hz,1H),
 20 7.62(dd,J=8.1Hz,1.2Hz,1H),7.58~7.53(m,2H),
 7.36(d,J=7.7Hz,1H),7.27~7.23(m,1H),7.15~7.11(m,1H),
 6.99(d,J=8.9Hz,1H),6.94(br s,1H),3.79(t,J=5.0Hz,4H),
 3.69~3.65(m,2H),3.51(s,3H),2.70(t,J=5.0Hz,4H),
 2.68~2.65(m,2H),1.95~1.92(m,2H)
 25 Mass,m/e:428(M⁺),157(base)

Production Example 1



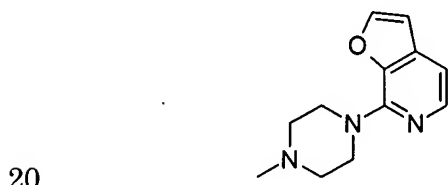
In 100 ml of ethylene glycol 8.6 g of anhydrous piperazine was dissolved, and to which 7-chlorofuro[2,3-c]pyridine was added,
 35 followed by an overnight's stirring at 140°C. After cooling,

saturated aqueous sodium hydrogencarbonate solution was added to the solution, which was then extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified
 5 on silica gel column chromatography to provide 1.52 g (75%) of 7-piperazin-1-ylfuro[2,3-c]pyridine.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.96(d, J=5.5Hz, 1H), 7.63(d, J=2.3Hz, 1H),
 6.97(d, J=5.4Hz, 1H), 6.72(d, J=1.9Hz, 1H), 3.83~3.80(m, 4H),
 10 3.06(t, J=5.0Hz, 4H)
 Mass, m/e: 203(M^+), 135(base)

Production Example 2

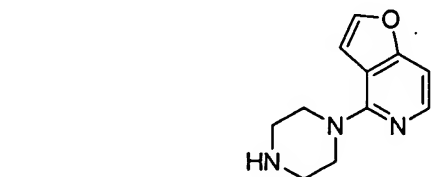
In the manner similar to Production Example 1,
 15 7-(4-methylpiperazin-1-yl)furo[2,3-c]pyridine was obtained.



$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.95(d, J=5.3Hz, 1H), 7.62(d, J=1.9Hz, 1H),
 6.96(d, J=5.4Hz, 1H), 6.72(d, J=1.9Hz, 1H), 3.88(t, J=5.0Hz, 4H),
 2.59(t, J=5.0Hz, 4H), 2.38(s, 3H)
 25 Mass, m/e: 217(M^+), 147(base)

Production Example 3

In the manner similar to Production Example 1,
 30 4-piperazin-1-ylfuro[3,2-c]pyridine was obtained.



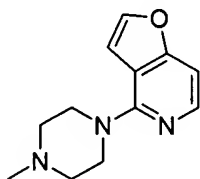
$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.05(d, $J=5.8\text{Hz}$, 1H), 7.53(d, $J=2.0\text{Hz}$, 1H),
 6.94(dd, $J=0.8\text{Hz}, 5.8\text{Hz}$, 1H), 6.81(dd, $J=1.2\text{Hz}, 2.3\text{Hz}$, 1H),
 3.67(t, $J=5.0\text{Hz}$, 4H), 3.05(t, $J=5.0\text{Hz}$, 4H)
 Mass, m/e : 203(M^+), 135(base)

5

Production Example 4

In the manner similar to Production Example 1,
 4-(4-methylpiperazin-1-yl)furo[2,3-c]pyridine was obtained.

10



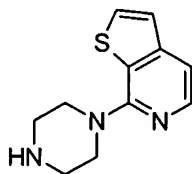
15

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.05(d, $J=5.8\text{Hz}$, 1H), 7.53(d, $J=2.3\text{Hz}$, 1H),
 6.94(dd, $J=1.2\text{Hz}, 5.8\text{Hz}$, 1H), 6.81(dd, $J=1.2\text{Hz}, 2.3\text{Hz}$, 1H),
 3.74(t, $J=5.0\text{Hz}$, 4H), 2.59(t, $J=5.0\text{Hz}$, 4H), 2.37(s, 3H)
 Mass, m/e : 217(M^+), 147(base)

20 Production Example 5

In the manner similar to Production Example 1,
 7-piperazin-1-ylthieno[2,3-c]pyridine was obtained.

25



30

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.14(d, $J=5.8\text{Hz}$, 1H), 7.58(d, $J=5.4\text{Hz}$, 1H),
 7.32(d, $J=5.4\text{Hz}$, 1H), 7.25(d, $J=5.4\text{Hz}$, 1H), 3.64(t, $J=5.0\text{Hz}$, 4H),
 3.09(t, $J=5.0\text{Hz}$, 4H)
 Mass, m/e : 219(M^+), 151(base)

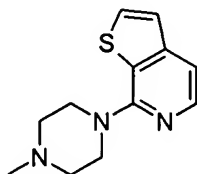
Production Example 6

35

In the manner similar to Production Example 1,

7-(4-methylpiperazin-1-yl)thieno[2,3-c]pyridine was obtained.

5



$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.13(d, $J=5.8\text{Hz}$, 1H), 7.57(d, $J=5.4\text{Hz}$, 1H),
7.31(d, $J=5.4\text{Hz}$, 1H), 7.24(d, $J=5.4\text{Hz}$, 1H), 3.71(t, $J=5.0\text{Hz}$, 4H),
2.63(t, $J=5.0\text{Hz}$, 4H), 2.38(s, 3H)

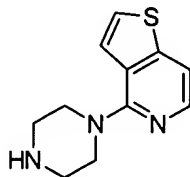
10

Mass, m/e : 233(M^+), 163(base)

Production Example 7

In the manner similar to Production Example 1,
4-piperazin-1-ylthieno[3,2-c]pyridine was obtained.

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20

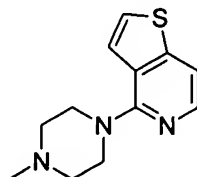
$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.09(d, $J=5.8\text{Hz}$, 1H), 7.42~7.35(m, 3H),
3.50(t, $J=5.0\text{Hz}$, 4H), 3.11(t, $J=5.0\text{Hz}$, 4H)

Mass, m/e : 219(M^+), 151(base)

Production Example 8

In the manner similar to Production Example 1,
4-(4-methylpiperazin-1-yl)thieno[3,2-c]pyridine was obtained.

30



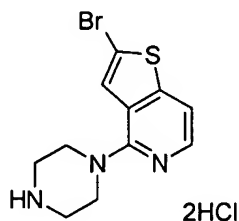
$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.08(d, $J=5.8\text{Hz}$, 1H), 7.41~7.33(m, 3H),
3.57(t, $J=5.0\text{Hz}$, 4H), 2.64(t, $J=5.0\text{Hz}$, 4H), 2.39(s, 3H)

Mass, m/e : 233(M^+), 163(base)

35

Production Example 9

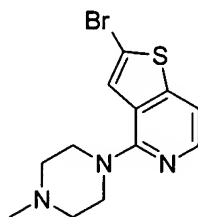
In the manner similar to Production Example 1,
2-bromo-4-piperazin-1-ylthieno[3,2-c]pyridine dihydrochloride was
obtained.



$^1\text{H-NMR}$ (DMSO- d_6) δ :8.03(d,J=5.8Hz,1H),7.90(s,1H),
7.67(d,J=5.8Hz,1H),3.72(br s,4H),2.59(br s,4H)
Mass,m/e:297(M^+),229(base)

Production Example 10

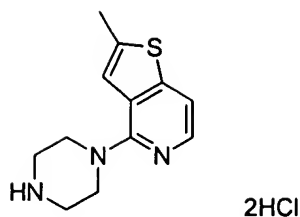
In the manner similar to Production Example 1,
2-bromo-4-(methylpiperazin-1-yl)thieno[3,2-c]pyridine was obtained.



$^1\text{H-NMR}$ (CDCl_3) δ :8.05(d,J=5.4Hz,1H),7.36(d,J=0.8Hz,1H),
7.19(dd,J=0.8Hz,5.8Hz,1H),3.53(t,J=5.0Hz,4H),
2.63(t,J=5.0Hz,4H),2.39(s,3H)
Mass,m/e:311(M^+),83(base)

Production Example 11

In the manner similar to Production Example 1,
2-methyl-4-piperazin-1-ylthieno[3,2-c]pyridine dihydrochloride was
obtained.



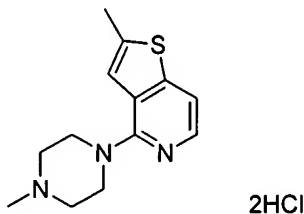
5

$^1\text{H-NMR}$ (DMSO- d_6) δ :7.94(d,J=6.2Hz,1H),7.76(d,J=6.2Hz,1H),
7.55(s,1H),3.91(br s,4H),2.59(br s,4H),2.64(s,3H)
Mass,m/e:233(M^+),177(base)

10 Production Example 12

In the manner similar to Production Example 1,
2-methyl-4-(4-methylpiperazin-1-yl)thieno[3,2-c]pyridine
dihydrochloride was obtained.

15



20

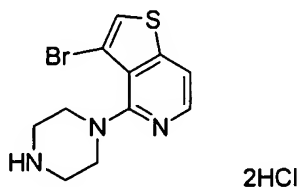
$^1\text{H-NMR}$ (DMSO- d_6) δ :7.96(d,J=6.2Hz,1H),7.73(d,J=5.8Hz,1H),
7.50(s,1H),4.20(d,J=5.9Hz,3H),3.57(br s,4H),3.30~3.27(m,4H),
2.84(d,J=4.3Hz,3H)
Mass,m/e:247(M^+),177(base)

25

Production Example 13

In the manner similar to Production Example 1,
3-bromo-4-piperazin-1-ylthieno[3,2-c]pyridine dihydrochloride was
obtained.

30



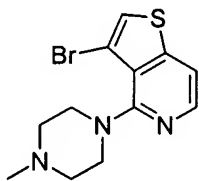
35

$^1\text{H-NMR}$ (DMSO- d_6) δ :8.17(d,J=5.4Hz,1H),8.02(s,1H),
7.83(d,J=5.8Hz,1H),3.56~3.32(m,8H)
Mass,m/e:297(M^+),229(base)

5 Production Example 14

In the manner similar to Production Example 1,
3-bromo-4-(4-methylpiperazin-1-yl)thieno[3,2-c]pyridine was
obtained.

10



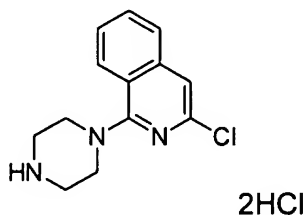
15

$^1\text{H-NMR}$ (DMSO- d_6) δ :8.17(d,J=5.4Hz,1H),8.03(s,1H),
7.84(d,J=5.4Hz,1H),3.59~3.51(m,4H),3.37~3.27(m,4H),
2.87(m,3H)
Mass,m/e:311(M^+),83(base)

20 Production Example 15

In the manner similar to Production Example 1,
3-chloro-1-piperazin-1-ylisoquinoline dihydrochloride was obtained.

25



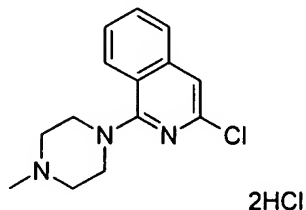
30

$^1\text{H-NMR}$ (DMSO- d_6) δ :8.08(d,J=8.5Hz,1H),7.90(d,J=8.1Hz,1H),
7.78~7.75(m,1H),7.64~7.62(m,1H),7.60(s,1H),3.60~3.57(m,4H),
3.29(br s,4H)
Mass,m/e:247(M^+),179(base)

35 Production Example 16

In the manner similar to Production Example 1,
3-chloro-1-(4-methylpiperazin-1-yl)isoquinoline dihydrochloride was
obtained.

5

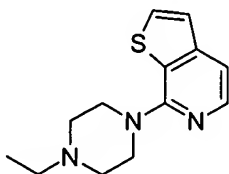


$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.02(d, $J=8.1\text{Hz}$, 1H), 7.90(d, $J=8.1\text{Hz}$, 1H),
7.79~7.75(m, 1H), 7.64(d, $J=7.3\text{Hz}$, 1H), 7.61(s, 1H),
3.98~3.52(m, 4H), 3.52~3.32(m, 4H), 2.86(m, 3H)
Mass, m/e : 261(M^+), 83(base)

15 Production Example 17

In the manner similar to Production Example 1,
7-(4-ethylpiperazin-1-yl)-thieno[2,3-c]pyridine was obtained.

20



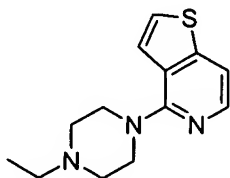
$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.12(d, $J=5.8\text{Hz}$, 1H), 7.57(d, $J=5.4\text{Hz}$, 1H),
7.31(d, $J=5.4\text{Hz}$, 1H), 7.23(d, $J=5.8\text{Hz}$, 1H), 3.73(t, $J=5.0\text{Hz}$, 4H),
2.67(t, $J=5.0\text{Hz}$, 4H), 2.52(q, $J=7.3\text{Hz}$, 2H), 1.53(t, $J=7.3\text{Hz}$, 3H)
Mass, m/e : 247(M^+), 163(base)

25

Production Example 18

In the manner similar to Production Example 1,
4-(4-ethylpiperazin-1-yl)thieno[3,2-c]pyridine was obtained.

30



35

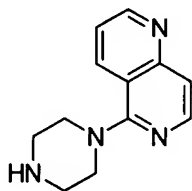
$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.08(d, $J=5.8\text{Hz}$, 1H), 7.41~7.33(m, 3H),
 3.59(t, $J=5.0\text{Hz}$, 4H), 2.68(t, $J=5.0\text{Hz}$, 4H), 2.52(q, $J=7.3\text{Hz}$, 2H),
 1.15(t, $J=7.3\text{Hz}$, 3H)
 Mass, m/e : 247(M^+), 163(base)

5

Production Example 19

In the manner similar to Production Example 1,
 5-piperazin-1-yl[1,6]naphthyridine was obtained.

10



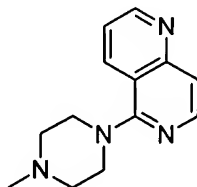
15

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.99(dd, $J=1.9\text{Hz}$, 4.2Hz, 1H),
 8.39(dd, $J=1.2\text{Hz}$, 8.5Hz, 1H), 8.34(d, $J=6.2\text{Hz}$, 1H),
 7.48(d, $J=6.2\text{Hz}$, 1H), 7.42(dd, $J=4.2\text{Hz}$, 8.5Hz, 1H),
 3.42~3.39(m, 4H), 3.16~3.14(m, 4H)
 Mass, m/e : 214(M^+), 146(base)

20 Production Example 20

In the manner similar to Production Example 1,
 5-(4-methylpiperazin-1-yl)[1,6]naphthyridine was obtained.

25



30

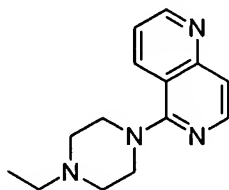
$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.98(dd, $J=1.9\text{Hz}$, 4.2Hz, 1H),
 8.39~8.36(m, 1H), 8.33(d, $J=6.2\text{Hz}$, 1H),
 7.48(dd, $J=0.8\text{Hz}$, 5.8Hz, 1H), 7.41(dd, $J=4.3\text{Hz}$, 5.8Hz, 1H),
 3.49(t, $J=5.0\text{Hz}$, 4H), 2.69(t, $J=5.0\text{Hz}$, 4H), 2.41(s, 3H)
 Mass, m/e : 228(M^+), 158(base)

35

Production Example 21

In the manner similar to Production Example 1,
5-(4-ethylpiperazin-1-yl)[1,6]naphthyridine was obtained.

5



10

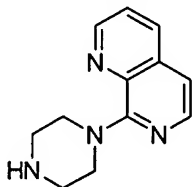
$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.97(dd, $J=1.9\text{Hz}, 4.2\text{Hz}$, 1H),
8.38~8.35(m, 1H), 8.32(d, $J=5.8\text{Hz}$, 1H), 7.46~7.45(m, 1H),
7.40(dd, $J=4.2\text{Hz}, 8.5\text{Hz}$, 1H), 3.49(t, $J=5.0\text{Hz}$, 4H),
2.71(t, $J=5.0\text{Hz}$, 4H), 2.54(q, $J=7.3\text{Hz}$, 2H), 1.15(t, $J=7.3\text{Hz}$, 3H)
Mass, m/e : 242(M^+), 158(base)

Production Example 22

15

In the manner similar to Production Example 1,
8-piperazin-1-yl[1,7]naphthyridine was obtained.

20



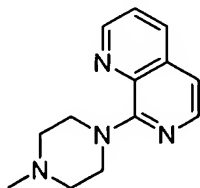
25

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.82(dd, $J=1.9\text{Hz}, 4.3\text{Hz}$, 1H),
8.13(d, $J=5.4\text{Hz}$, 1H), 8.00(dd, $J=1.9\text{Hz}, 8.5\text{Hz}$, 1H),
7.47(dd, $J=4.2\text{Hz}, 8.5\text{Hz}$, 1H), 7.04(d, $J=5.8\text{Hz}$, 1H),
3.93(t, $J=5.0\text{Hz}$, 4H), 3.13(t, $J=5.0\text{Hz}$, 4H)
Mass, m/e : 214(M^+), 146(base)

Production Example 23

In the manner similar to Production Example 1,
8-(4-methylpiperazin-1-yl)[1,7]naphthyridine was obtained.

30



35

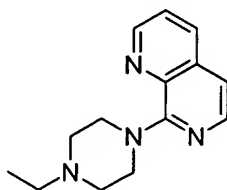
$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.82(dd, $J=1.9\text{Hz}, 4.3\text{Hz}$, 1H),
 8.12(d, $J=5.8\text{Hz}$, 1H), 7.80(dd, $J=1.9\text{Hz}, 8.5\text{Hz}$, 1H),
 7.47(dd, $J=4.2\text{Hz}, 8.5\text{Hz}$, 1H), 7.04(d, $J=5.4\text{Hz}$, 1H),
 4.01(br s, 4H), 2.67(t, $J=5.0\text{Hz}$, 4H), 2.38(s, 3H)

5 Mass, m/e : 228(M^+), 158(base)

Production Example 24

In the manner similar to Production Example 1,
 8-(4-ethylpiperazin-1-yl)[1,7]naphthyridine was obtained.

10



15

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.81(dd, $J=1.9\text{Hz}, 4.2\text{Hz}$, 1H),
 8.16(d, $J=5.4\text{Hz}$, 1H), 7.99(dd, $J=1.9\text{Hz}, 8.5\text{Hz}$, 1H),
 7.47(dd, $J=4.2\text{Hz}, 8.5\text{Hz}$, 1H), 7.03(d, $J=5.4\text{Hz}$, 1H),
 4.03(t, $J=4.6\text{Hz}$, 4H), 2.71(t, $J=4.6\text{Hz}$, 4H), 2.51(q, $J=7.3\text{Hz}$, 2H),
 1.15(t, $J=7.3\text{Hz}$, 3H)

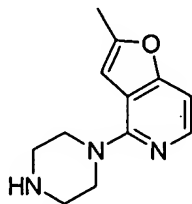
20

Mass, m/e : 242(M^+), 158(base)

Production Example 25

In the manner similar to Production Example 1,
 25 2-methylpiperazin-1-ylfuro[3,2-c]pyridine was obtained.

30



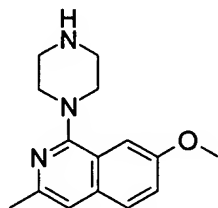
$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.93(d, $J=5.8\text{Hz}$, 1H),
 6.86(dd, $J=1.2\text{Hz}, 5.8\text{Hz}$, 1H), 6.38(s, 1H), 3.60(t, $J=5.0\text{Hz}$, 4H),
 3.03(t, $J=5.0\text{Hz}$, 4H), 2.43(d, $J=1.2\text{Hz}$, 3H)

Mass, m/e : 217(M^+), 161(base)

35

Production Example 26

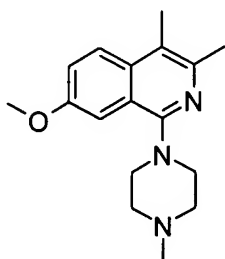
In the manner similar to Production Example 1,
7-methoxy-3-methyl-1-piperazin-1-ylisoquinoline was obtained.



$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.58(d, $J=8.9\text{Hz}$, 1H), 7.36(d, $J=2.3\text{Hz}$, 1H),
7.23(dd, $J=2.3\text{Hz}$, 8.9Hz, 1H), 7.05(s, 1H), 3.92(s, 3H),
3.36~3.32(m, 4H), 3.18~3.14(m, 4H), 2.54(s, 3H)
Mass, m/e : 257(M^+), 188(Base)

Production Example 27

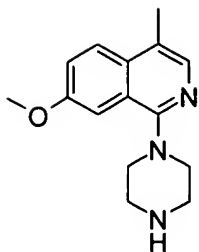
In the manner similar to Production Example 1,
7-methoxy-3,4-dimethyl-1-(4-methylpiperazin-1-yl)isoquinoline was
obtained.



$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.82(d, $J=9.2\text{Hz}$, 1H), 7.41(d, $J=2.7\text{Hz}$, 1H),
7.27(dd, $J=2.7\text{Hz}$, 9.2Hz, 1H), 3.93(s, 3H), 3.41~3.34(m, 4H),
2.73~2.68(m, 4H), 2.56(s, 3H), 2.46(s, 3H), 2.41(s, 3H)
Mass, m/e : 285(M^+), 215(base), 202

Production Example 28

In the manner similar to Production Example 1,
7-methoxy-4-methyl-1-piperazin-1-ylisoquinoline was obtained.



5

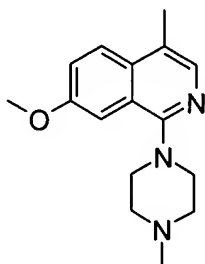
$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.92(d, $J=0.7\text{Hz}$, 1H), 7.81(d, $J=9.2\text{Hz}$, 1H),
7.49(d, $J=2.7\text{Hz}$, 1H), 7.40(dd, $J=2.7\text{Hz}$, 9.2Hz, 1H), 3.95(s, 3H),
3.31~3.26(m, 4H), 3.18~3.14(m, 4H), 2.49(d, $J=0.7\text{Hz}$, 3H)

10

Mass, m/e : 257(M^+), 201, 188(base)

Production Example 29

In the manner similar to Production Example 1,
7-methoxy-4-methyl-1-(4-methylpiperazin-1-yl)isoquinoline was
15 obtained.



20

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.90(s, 1H), 7.80(d, $J=9.3\text{Hz}$, 1H),
7.45(d, $J=2.7\text{Hz}$, 1H), 7.33(dd, $J=2.7\text{Hz}$, 9.3Hz, 1H), 3.95(s, 3H),
3.48~3.39(m, 4H), 2.75~2.66(m, 4H), 2.49(s, 3H), 2.41(s, 3H)

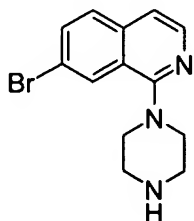
25

Mass, m/e : 305(M^+), 235, 83(base)

Production Example 30

In the manner similar to Production Example 1,
7-bromo-1-piperazin-1-ylisoquinoline was obtained.

30



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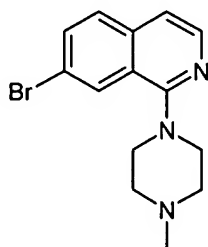
$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.24~8.22(m, 1H), 8.16(d, $J=5.8\text{Hz}$, 1H),
 7.67(dd, $J=1.9\text{Hz}, 8.5\text{Hz}$, 1H), 7.61(d, $J=8.9\text{Hz}$, 1H),
 7.26~7.19(m, 1H), 3.36~3.32(m, 4H), 3.16~3.12(m, 4H)
 Mass, m/e : 292(M^+), 235, 223(base)

5

Production Example 31

In the manner similar to Production Example 1,
 7-bromo-1-(4-methylpiperazin-1-yl)isoquinoline was obtained.

10



15

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.23~8.21(m, 1H), 8.16(d, $J=5.8\text{Hz}$, 1H),
 7.67(dd, $J=1.9\text{Hz}, 8.5\text{Hz}$, 1H), 7.61(d, $J=8.5\text{Hz}$, 1H),
 7.20(dd, $J=0.8\text{Hz}, 5.8\text{Hz}$), 3.47~3.39(m, 4H), 2.76~2.26(m, 4H),
 2.41(s, 3H)

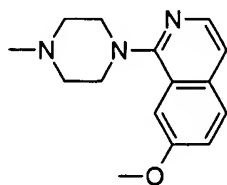
20

Mass, m/e : 305(M^+), 235, 83(base)

Production Example 32

In the manner similar to Production Example 1,
 7-methoxy-1-(4-methylpiperazin-1-yl)isoquinoline was obtained.

25



30

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.07(d, $J=5.8\text{Hz}$, 1H), 7.68(d, $J=8.9\text{Hz}$, 1H),
 7.39(d, $J=2.7\text{Hz}$, 1H), 7.29(dd, $J=2.7\text{Hz}, 8.9\text{Hz}$, 1H),
 7.22(d, $J=5.8\text{Hz}$, 1H), 3.94(s, 3H), 3.48~3.40(m, 4H),
 2.77~2.69(m, 4H)

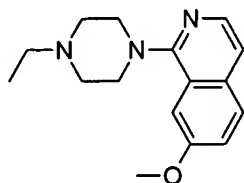
35

Mass, m/e : 257(M^+), 187(base)

Production Example 33

In the manner similar to Production Example 1,
1-(4-ethylpiperazin-1-yl)-7-methoxyisoquinoline was obtained.

5



10

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.07(d, $J=5.8\text{Hz}$, 1H), 7.68(d, $J=8.7\text{Hz}$, 1H),
7.40(d, $J=2.5\text{Hz}$, 1H), 7.31~7.25(m, 1H), 7.21(d, $J=5.8\text{Hz}$, 1H),
3.48~3.39(m, 4H), 2.79~2.69(m, 4H), 2.55(q, $J=7.2\text{Hz}$, 2H),
1.17(t, $J=7.2\text{Hz}$, 3H)

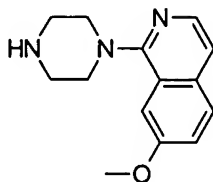
15

Mass, m/e : 271(M^+), 187(base)

Production Example 34

In the manner similar to Production Example 1,
7-methoxy-1-piperazin-1-ylisoquinoline was obtained.

20



25

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.08(d, $J=5.5\text{Hz}$, 1H), 7.68(d, $J=9.2\text{Hz}$, 1H),
7.42(d, $J=2.6\text{Hz}$, 1H), 7.29(dd, $J=2.6\text{Hz}$, 9.2Hz, 1H),
7.23(d, $J=5.5\text{Hz}$, 1H), 3.94(s, 3H), 3.37~3.30(m, 4H),
3.20~3.13(m, 4H)

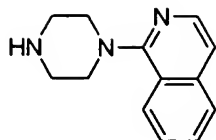
30

Mass, m/e : 243(M^+), 174(base)

Production Example 35

In the manner similar to Production Example 1,
1-piperazin-1-ylisoquinoline was obtained.

35



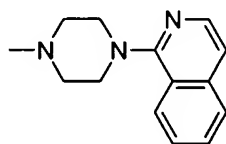
5 $^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.15(d, $J=5.9\text{Hz}$, 1H), 8.11(d, $J=8.4\text{Hz}$, 1H),
 7.75(d, $J=8.1\text{Hz}$, 1H), 7.61(ddd, $J=1.1\text{Hz}$, 7.0Hz, 8.1Hz, 1H),
 7.51(ddd, 1.1Hz, 7.0Hz, 8.4Hz, 1H), 7.25(d, $J=5.9\text{Hz}$, 1H),
 3.41~3.34(m, 4H), 3.18~3.13(m, 4H)
 Mass, m/e : 213(M^+), 145(base)

10

Production Example 36

In the manner similar to Production Example 1,
 1-(4-methylpiperazin-1-yl)isoquinoline was obtained.

15



20

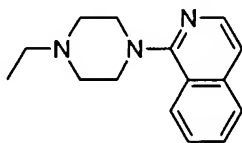
$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.15(d, $J=5.9\text{Hz}$, 1H), 8.09(d, $J=8.4\text{Hz}$, 1H),
 7.75(d, $J=8.1\text{Hz}$, 1H), 7.60(ddd, $J=1.1\text{Hz}$, 7.0Hz, 8.1Hz, 1H),
 7.50(ddd, 1.1Hz, 7.0Hz, 8.4Hz, 1H), 7.24(d, $J=5.9\text{Hz}$, 1H),
 3.51~3.41(m, 4H), 2.74~2.66(m, 4H), 2.42(s, 3H)
 Mass, m/e : 227(M^+), 157(base)

Production Example 37

25

In the manner similar to Production Example 1,
 1-(4-ethylpiperazin-1-yl)isoquinoline was obtained.

30



35

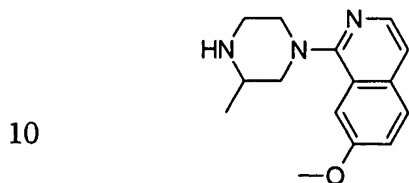
$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.14(d, $J=5.9\text{Hz}$, 1H), 8.09(d, $J=8.4\text{Hz}$, 1H),
 7.74(d, $J=8.1\text{Hz}$, 1H), 7.60(ddd, $J=1.1\text{Hz}$, 7.0Hz, 8.1Hz, 1H),
 7.50(ddd, 1.1Hz, 7.0Hz, 8.4Hz, 1H), 7.23(d, $J=5.9\text{Hz}$, 1H),
 3.51~3.44(m, 4H), 2.77~2.69(m, 4H), 2.55(q, $J=7.3\text{Hz}$, 2H),

1.17(t, J=7.3Hz, 3H)

Mass, m/e: 241(M⁺), 157(base)

Production Example 38

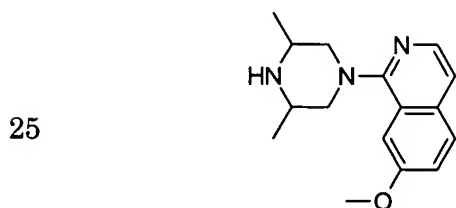
5 In the manner similar to Production Example 1,
7-methoxy-1-(3-methylpiperazin-1-yl)isoquinoline was obtained.



¹H-NMR(CDCl₃)δ: 8.07(d, J=5.8Hz, 1H), 7.68(d, J=8.9Hz, 1H),
7.40(d, J=2.7Hz, 1H), 7.29(dd, J=2.7Hz, 8.9Hz, 1H),
7.23(d, J=5.8Hz, 1H), 3.94(s, 3H), 3.70~3.62(m, 2H),
15 3.30~3.17(m, 3H), 3.08~2.99(m, 1H), 2.80~2.71(m, 1H),
1.20(d, J=6.6Hz, 3H)
Mass, m/e: 257(M⁺), 175(base)

Production Example 39

20 In the manner similar to Production Example 1,
1-(3,5-dimethylpiperazin-1-yl)-7-methoxyisoquinoline was obtained.



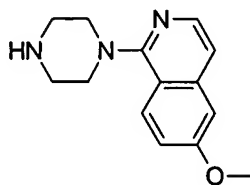
¹H-NMR(CDCl₃)δ: 8.07(d, J=5.8Hz, 1H), 7.68(d, J=8.9Hz, 1H),
7.40(d, J=2.7Hz, 1H), 7.29(dd, J=2.7Hz, 8.9Hz, 1H),
30 7.21(d, J=5.8Hz, 1H), 3.93(s, 3H), 3.70~3.62(m, 2H),
3.33~3.23(m, 2H), 2.66~2.57(m, 2H), 1.17(d, J=6.6Hz, 6H)
Mass, m/e: 271(M⁺), 187(base)

Production Example 40

35 In the manner similar to Production Example 1,

6-methoxy-1-piperazin-1-ylisoquinoline was obtained.

5



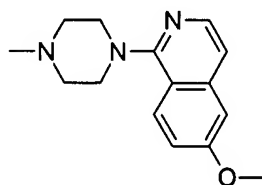
10

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.10(d, $J=5.9\text{Hz}$, 1H), 8.01(d, $J=9.2\text{Hz}$, 1H),
 7.16(d, $J=5.9\text{Hz}$, 1H), 7.13(dd, $J=2.6\text{Hz}$, 9.2Hz, 1H),
 7.02(d, $J=2.6\text{Hz}$, 1H), 3.93(s, 3H), 3.38~3.32(m, 4H),
 3.18~3.12(m, 4H)
 Mass, m/e : 243(M^+), 187(base)

Production Example 41

In the manner similar to Production Example 1,
 15 6-methoxy-1-(4-methylpiperazin-1-yl)isoquinoline was obtained.

20



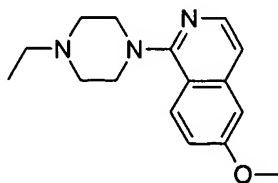
25

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.09(d, $J=5.9\text{Hz}$, 1H), 7.99(d, $J=9.2\text{Hz}$, 1H),
 7.15(d, $J=5.9\text{Hz}$, 1H), 7.12(dd, $J=2.6\text{Hz}$, 9.2Hz, 1H),
 7.02(d, $J=2.6\text{Hz}$, 1H), 3.93(s, 3H), 3.48~3.38(m, 4H),
 2.74~2.64(m, 4H), 2.41(s, 3H)
 Mass, m/e : 257(M^+), 187(base)

Production Example 42

In the manner similar to Production Example 1,
 1-(4-ethylpiperazin-1-yl)-6-methoxyisoquinoline was obtained.

30



35

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.09(d, $J=5.9\text{Hz}$, 1H), 7.99(d, $J=9.2\text{Hz}$, 1H),

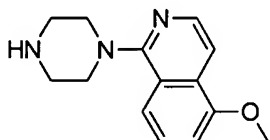
7.14(d, J=5.9Hz, 1H), 7.11(dd, J=2.6Hz, 9.2Hz, 1H),
 7.01(d, J=2.6Hz, 1H), 3.93(s, 3H), 3.48~3.38(m, 4H),
 2.76~2.67(m, 4H), 2.55(q, J=7.3Hz, 2H), 1.16(t, J=7.3Hz, 3H)
 Mass, m/e: 271(M⁺), 187(base)

5

Production Example 43

In the manner similar to Production Example 1,
 5-methoxy-1-piperazin-1-ylisoquinoline was obtained.

10



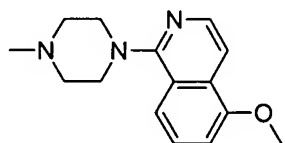
15

¹H-NMR(CDCl₃) δ: 8.16(d, J=6.2Hz, 1H), 7.67(d, J=8.5Hz, 1H),
 7.63(dd, J=0.8Hz, 5.8Hz, 1H), 7.41(t, J=7.7Hz, 1H),
 6.94(d, J=7.7Hz, 1H), 3.99(s, 3H), 3.39~3.31(m, 4H),
 3.18~3.11(m, 4H)
 Mass, m/e: 243(M⁺), 174(base)

20 Production Example 44

In the manner similar to Production Example 1,
 5-methoxy-1-(4-methylpiperazin-1-yl)isoquinoline was obtained.

25



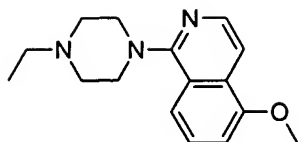
30

¹H-NMR(CDCl₃) δ: 8.16(d, J=5.8Hz, 1H),
 7.65(dd, J=0.8Hz, 8.5Hz, 1H), 7.62(dd, J=0.8Hz, 5.8Hz, 1H),
 7.41(t, J=7.7Hz, 1H), 6.94(d, J=7.7Hz, 1H), 3.98(s, 3H),
 3.50~3.38(m, 4H), 2.74~2.63(m, 4H), 2.41(s, 3H)
 Mass, m/e: 257(M⁺), 187(base)

Production Example 45

In the manner similar to Production Example 1,
 1-(4-ethylpiperazin-1-yl)-5-methoxyisoquinoline was obtained.

35



5

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.15(d, $J=5.8\text{Hz}$, 1H), 7.65(d, $J=8.5\text{Hz}$, 1H),
 7.62(d, $J=5.8\text{Hz}$, 1H), 7.40(t, $J=7.7\text{Hz}$, 1H), 6.93(d, $J=7.7\text{Hz}$, 1H),
 3.98(s, 3H), 3.50~3.40(m, 4H), 2.77~2.68(m, 4H),
 2.55(q, $J=7.3\text{Hz}$, 2H), 1.16(t, $J=7.3\text{Hz}$, 3H)

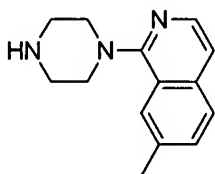
10

Mass, m/e : 271(M^+), 187(base)

Production Example 46

In the manner similar to Production Example 1,
 7-methyl-1-piperazin-1-ylisoquinoline was obtained.

15



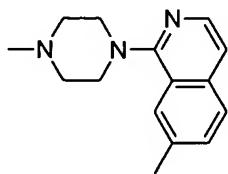
20

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.10(d, $J=5.8\text{Hz}$, 1H), 7.88(s, 1H),
 7.66(d, $J=8.1\text{Hz}$, 1H), 7.45(dd, $J=1.5\text{Hz}$, 8.1Hz, 1H),
 7.22(d, $J=5.8\text{Hz}$, 1H), 3.39~3.32(m, 4H), 3.20~3.13(m, 4H)
 Mass, m/e : 227(M^+), 159(base)

Production Example 47

In the manner similar to Production Example 1,
 7-methyl-1-(4-methylpiperazin-1-yl)isoquinoline was obtained.

30



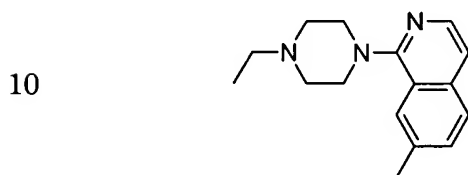
35

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.09(d, $J=5.8\text{Hz}$, 1H), 7.85(s, 1H),
 7.65(d, $J=8.5\text{Hz}$, 1H), 7.44(dd, $J=1.5\text{Hz}$, 8.5Hz, 1H),

7.21(d, J=5.8Hz, 1H), 3.51~3.38(m, 4H), 2.77~2.64(m, 4H),
 2.54(s, 3H), 2.42(s, 3H)
 Mass, m/e: 241(M⁺), 171(base)

5 Production Example 48

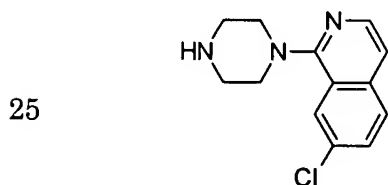
In the manner similar to Production Example 1,
 1-(4-ethylpiperazin-1-yl)-7-methylisoquinoline was obtained.



¹H-NMR(CDCl₃) δ: 8.09(d, J=5.8Hz, 1H), 7.85(s, 1H),
 7.65(d, J=8.5Hz, 1H), 7.44(dd, J=1.5Hz, 8.5Hz, 1H),
 15 7.20(d, J=5.8Hz, 1H), 3.50~3.40(m, 4H), 2.80~2.69(m, 4H),
 2.59~2.52(m, 5H), 1.17(t, J=7.3Hz, 3H)
 Mass, m/e: 255(M⁺), 171(base)

Production Example 49

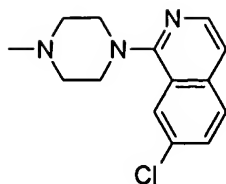
20 In the manner similar to Production Example 1,
 7-chloro-1-piperazin-1-ylisoquinoline was obtained.



¹H-NMR(CDCl₃) δ: 8.16(d, J=5.8Hz, 1H), 8.07(d, J=1.9Hz, 1H),
 7.70(d, J=8.5Hz, 1H), 7.55(dd, J=1.9Hz, 8.5Hz, 1H),
 30 7.23(d, J=5.8Hz, 1H), 3.41~3.33(m, 4H), 3.20~3.14(m, 4H)
 Mass, m/e: 247(M⁺), 179(base)

Production Example 50

In the manner similar to Production Example 1,
 35 7-chloro-1-(4-methylpiperazin-1-yl)isoquinoline was obtained.



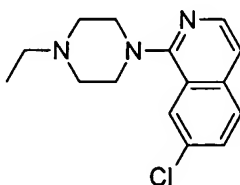
5

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.15(d, $J=5.8\text{Hz}$, 1H), 8.05(d, $J=1.9\text{Hz}$, 1H),
 7.70(d, $J=8.5\text{Hz}$, 1H), 7.55(dd, $J=1.9\text{Hz}$, 8.5Hz, 1H),
 7.22(d, $J=5.8\text{Hz}$, 1H), 3.48~3.40(m, 4H), 2.77~2.70(m, 4H),
 2.42(s, 3H)
 Mass, m/e : 261(M^+), 83(base)

10

Production Example 51

In the manner similar to Production Example 1,
 15 7-chloro-1-(4-ethylpiperazin-1-yl)isoquinoline was obtained.



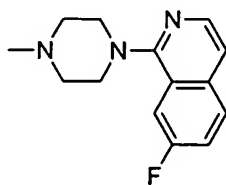
20

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.15(d, $J=5.8\text{Hz}$, 1H), 8.05(d, $J=1.9\text{Hz}$, 1H),
 7.70(d, $J=8.5\text{Hz}$, 1H), 7.55(dd, $J=1.9\text{Hz}$, 8.5Hz, 1H),
 7.21(d, $J=5.8\text{Hz}$, 1H), 3.49~3.40(m, 4H), 2.79~2.69(m, 4H),
 2.56(q, $J=7.3\text{Hz}$, 2H), 1.17(t, $J=7.3\text{Hz}$, 3H)
 25 Mass, m/e : 275(M^+), 97(base)

Production Example 52

In the manner similar to Production Example 1,
 30 7-fluoro-1-(4-methylpiperazin-1-yl)isoquinoline was obtained.

35



35

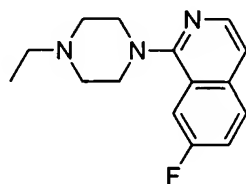
$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.14(d, $J=5.8\text{Hz}$, 1H), 7.78~7.73(m, 1H),
 7.73~7.66(m, 1H), 7.42~7.35(m, 1H), 7.24(d, $J=5.8\text{Hz}$, 1H),
 3.48~3.37(m, 4H), 2.76~2.64(m, 4H), 2.42(s, 3H)
 Mass, m/e : 245(M^+), 175(base)

5

Production Example 53

In the manner similar to Production Example 1,
 1-(4-ethylpiperazin-1-yl)-7-fluoroisoquinoline was obtained.

10



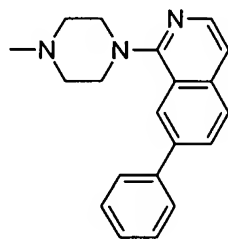
15

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.14(d, $J=5.8\text{Hz}$, 1H), 7.78~7.73(m, 1H),
 7.73~7.67(m, 1H), 7.42~7.36(m, 1H), 7.24(d, $J=5.8\text{Hz}$, 1H),
 3.49~3.39(m, 4H), 2.79~2.70(m, 4H), 2.56(q, $J=7.3\text{Hz}$, 2H),
 1.17(t, $J=7.3\text{Hz}$, 3H)
 Mass, m/e : 259(M^+), 175(base)

20 Production Example 54

In the manner similar to Production Example 1,
 1-(4-methylpiperazin-1-yl)-7-phenylisoquinoline was obtained.

25



30

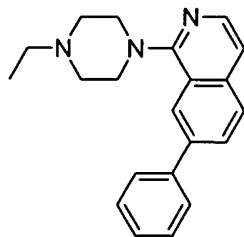
$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.30~8.27(m, 1H), 8.16(d, $J=5.8\text{Hz}$, 1H),
 7.90~7.80(m, 2H), 7.72~7.67(m, 2H), 7.55~7.48(m, 2H),
 7.44~7.39(m, 1H), 7.29~7.25(m, 1H), 3.55~3.49(m, 4H),
 2.76~2.66(m, 4H), 2.42(s, 3H)
 Mass, m/e : 303(M^+), 233(base)

35

Production Example 55

In the manner similar to Production Example 1,
1-(4-ethylpiperazin-1-yl)-7-phenylisoquinoline was obtained.

5



10

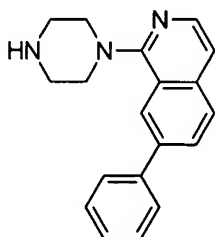
$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.30~8.27(m, 1H), 8.16(d, $J=5.8\text{Hz}$, 1H),
7.89~7.80(m, 2H), 7.72~7.67(m, 2H), 7.55~7.49(m, 2H),
7.44~7.39(m, 1H), 7.28~7.24(m, 1H), 3.58~3.48(m, 4H),
2.81~2.72(m, 4H), 2.56(q, $J=7.3\text{Hz}$, 2H), 1.17(t, $J=7.3\text{Hz}$, 3H)
Mass, m/e : 317(M^+), 233(base)

15

Production Example 56

In the manner similar to Production Example 1,
7-phenyl-1-piperazin-1-ylisoquinoline was obtained.

20



25

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.30(s, 1H), 8.16(d, $J=5.8\text{Hz}$, 1H),
7.90~7.80(m, 2H), 7.72~7.67(m, 2H), 7.54~7.48(m, 2H),
7.44~7.39(m, 1H), 7.28(d, $J=5.8\text{Hz}$, 1H), 3.47~3.38(m, 4H),
3.21~3.14(m, 4H)

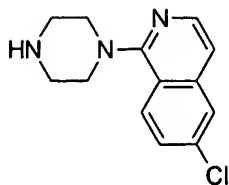
30

Mass, m/e : 289(M^+), 220(base)

Production Example 57

In the manner similar to Production Example 1,
6-chloro-1-piperazin-1-ylisoquinoline was obtained.

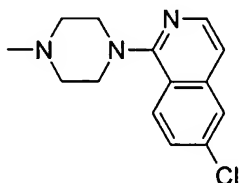
35



5 $^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.16(d, $J=5.8\text{Hz}$, 1H), 8.03(d, $J=8.9\text{Hz}$, 1H),
 7.73(d, $J=1.9\text{Hz}$, 1H), 7.44(dd, $J=1.9\text{Hz}$, 8.9Hz, 1H),
 7.16(d, $J=5.8\text{Hz}$, 1H), 3.40~3.34(m, 4H), 3.17~3.12(m, 4H)
 Mass, m/e : 247(M^+), 179(base)

10 Production Example 58

In the manner similar to Production Example 1,
 6-chloro-1-(4-methylpiperazin-1-yl)isoquinoline was obtained.

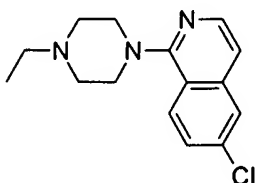


15

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.15(d, $J=5.8\text{Hz}$, 1H), 8.01(d, $J=8.9\text{Hz}$, 1H),
 7.72(d, $J=1.9\text{Hz}$, 1H), 7.43(dd, $J=1.9\text{Hz}$, 8.9Hz, 1H),
 20 7.14(d, $J=5.8\text{Hz}$, 1H), 3.45(t, $J=4.6\text{Hz}$, 4H), 2.69(t, $J=4.6\text{Hz}$, 4H),
 2.41(s, 3H)
 Mass, m/e : 261(M^+), 83(base)

Production Example 59

25 In the manner similar to Production Example 1,
 6-chloro-1-(4-ethylpiperazin-1-yl)isoquinoline was obtained.



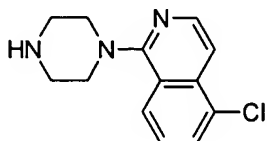
30

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.15(d, $J=5.8\text{Hz}$, 1H), 8.01(d, $J=8.9\text{Hz}$, 1H),
 7.72(d, $J=1.9\text{Hz}$, 1H), 7.42(dd, $J=1.9\text{Hz}$, 8.9Hz, 1H),
 7.14(d, $J=5.8\text{Hz}$, 1H), 3.46(t, $J=4.6\text{Hz}$, 4H), 2.72(t, $J=4.6\text{Hz}$, 4H),
 35 2.55(q, $J=7.3\text{Hz}$, 2H), 1.16(t, $J=7.3\text{Hz}$, 3H)

Mass, m/e: 275(M⁺), 83(base)

Production Example 60

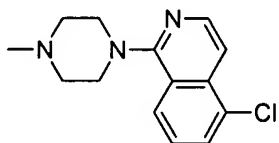
In the manner similar to Production Example 1,
5-chloro-1-piperazin-1-ylisoquinoline was obtained.



¹H-NMR(CDCl₃) δ: 8.25(d, J=5.8Hz, 1H),
8.04(td, J=1.2Hz, 8.5Hz, 1H), 7.69(dd, J=1.2Hz, 7.3Hz, 1H),
7.64(dd, J=1.2Hz, 5.8Hz, 1H), 7.42(dd, J=7.3Hz, 8.5Hz, 1H),
3.41~3.35(m, 4H), 3.18~3.13(m, 4H)
Mass, m/e: 247(M⁺), 179(base)

Production Example 61

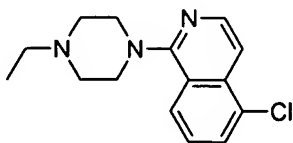
In the manner similar to Production Example 1,
5-chloro-1-(4-methylpiperazin-1-yl)isoquinoline was obtained.



¹H-NMR(CDCl₃) δ: 8.24(d, J=5.8Hz, 1H), 8.02(d, J=8.5Hz, 1H),
7.68(dd, J=1.2Hz, 7.3Hz, 1H), 7.62(dd, J=1.2Hz, 5.8Hz, 1H),
7.41(dd, J=7.3Hz, 8.5Hz, 1H), 3.45(t, J=4.6Hz, 4H),
2.69(t, J=4.6Hz, 4H), 2.41(s, 3H)
Mass, m/e: 261(M⁺), 83(base)

Production Example 62

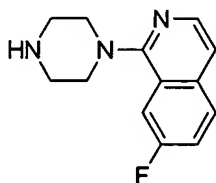
In the manner similar to Production Example 1,
5-chloro-1-(4-ethylpiperazin-1-yl)isoquinoline was obtained.



$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.24(d, $J=5.8\text{Hz}$, 1H), 8.02(d, $J=8.5\text{Hz}$, 1H),
 7.68(dd, $J=0.8\text{Hz}$, 7.3Hz, 1H), 7.61(d, $J=6.2\text{Hz}$, 1H),
 7.40(t, $J=8.1\text{Hz}$, 1H), 3.47(t, $J=4.6\text{Hz}$, 4H), 2.73(t, $J=4.6\text{Hz}$, 4H),
 2.55(q, $J=7.3\text{Hz}$, 2H), 1.16(t, $J=7.3\text{Hz}$, 3H)
 Mass, m/e : 275(M^+), 97(base)

Production Example 63

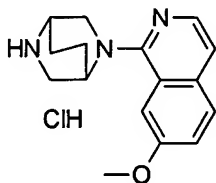
In the manner similar to Production Example 1,
 7-fluoro-1-piperazin-1-ylisoquinoline was obtained.



$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.14(d, $J=5.8\text{Hz}$, 1H), 7.79~7.69(m, 2H),
 7.43~7.37(m, 1H), 7.27~7.24(m, 1H), 3.38~3.32(m, 4H),
 3.19~3.14(m, 4H)
 Mass, m/e : 231(M^+), 163(base)

Production Example 64

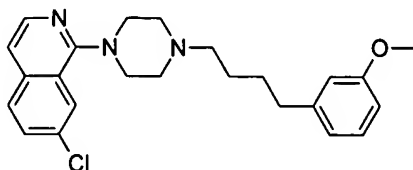
In the manner similar to Production Example 1,
 1-(2,5-diazabicyclo[2.2.2]octan-1-yl)-7-methoxyisoquinoline was
 obtained.



$^1\text{H-NMR}(\text{DMSO}-d_6)\delta$: 7.97(d, $J=8.9\text{Hz}$, 1H), 7.79(d, $J=6.2\text{Hz}$, 1H),
 7.59(d, $J=8.9\text{Hz}$, 1H), 7.48(s, 1H), 7.42(d, $J=6.2\text{Hz}$, 1H),
 4.63(br s, 1H), 4.42~4.31(m, 1H), 4.10~3.98(m, 1H), 3.96(s, 3H),
 3.96~3.27(m, 3H), 2.48~2.37(m, 1H), 2.28~2.13(m, 1H),
 2.08~1.92(m, 2H)
 Mass, m/e : 269(M^+), 175(base)

Production Example 65

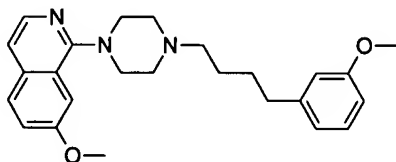
In the manner similar to Production Example 1,
7-chloro-1-[4-[4-(3-methoxyphenyl)butyl]piperazin-1-yl]isoquinoline
5 was obtained.



10 $^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.15(d, $J=5.8\text{Hz}$, 1H), 8.06(m, 1H),
7.67(d, $J=8.9\text{Hz}$, 1H), 7.56(d, $J=1.9\text{Hz}$, 1H), 7.52(d, $J=2.3\text{Hz}$, 1H),
7.26(t, $J=3.9\text{Hz}$, 1H), 6.82(d, $J=7.7\text{Hz}$, 1H), 6.75~6.69(m, 2H),
3.86(s, 3H), 3.39(t, $J=5.0\text{Hz}$, 4H), 2.69(t, $J=4.8\text{Hz}$, 4H),
2.59(t, $J=7.0\text{Hz}$, 2H), 2.41(t, $J=7.5\text{Hz}$, 2H), 1.75~1.50(m, 4H)
15 Mass, m/e : 409(M^+), 191(base), 121, 107

Production Example 66

In the manner similar to Production Example 1,
7-methoxy-1-[4-[4-(3-methoxyphenyl)butyl]piperazin-1-yl]-
20 isoquinoline was obtained.

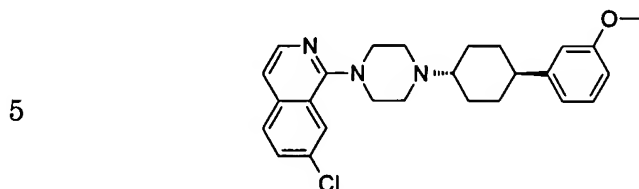


25 $^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.17(d, $J=5.9\text{Hz}$, 1H), 8.08(s, 1H),
7.20(d, $J=8.9\text{Hz}$, 1H), 7.13(d, $J=1.9\text{Hz}$, 1H), 7.10(d, $J=2.3\text{Hz}$, 1H),
7.04(t, $J=3.9\text{Hz}$, 1H), 6.80(d, $J=7.6\text{Hz}$, 1H),
6.79~6.65(m, 2H), 3.96(s, 3H), 3.89(s, 3H), 3.42(t, $J=4.8\text{Hz}$, 4H),
30 2.73(t, $J=4.8\text{Hz}$, 4H), 2.63(t, $J=6.9\text{Hz}$, 2H), 2.43(t, $J=7.5\text{Hz}$, 2H),
1.78~1.47(m, 4H)
Mass, m/e : 405(M^+), 187(base), 121, 107

Production Example 67

35 In the manner similar to Production Example 1,

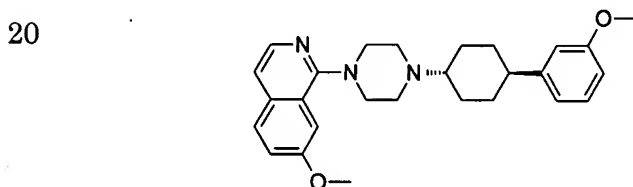
7-chloro-1-[4-[trans-4-(3-methoxyphenyl)cyclohexan-1-yl]piperazin-1-yl]isoquinoline was obtained.



$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.14(d, $J=5.8\text{Hz}$, 1H), 8.03(m, 1H),
 7.69(d, $J=8.9\text{Hz}$, 1H), 7.55(d, $J=1.9\text{Hz}$, 1H), 7.53(d, $J=1.9\text{Hz}$, 1H),
 10 7.22(d, $J=5.9\text{Hz}$, 1H), 6.81(d, $J=7.7\text{Hz}$, 1H), 6.76~6.72(m, 2H),
 3.80(s, 3H), 3.59(t, $J=5.0\text{Hz}$, 4H), 2.97(t, $J=4.8\text{Hz}$, 4H),
 2.53~2.47(m, 2H), 2.21~2.10(m, 4H), 2.09~2.00(m, 4H)
 Mass, m/e : 435(M^+), 420, 191(base), 121, 107

15 Production Example 68

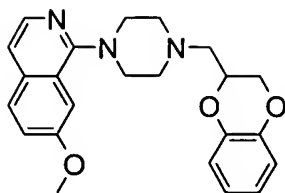
In the manner similar to Production Example 1,
 7-methoxy-1-[4-[trans-4-(3-methoxyphenyl)cyclohexan-1-yl]-
 piperazin-1-yl]isoquinoline was obtained.



$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.08(d, $J=5.7\text{Hz}$, 1H), 8.00(d, $J=9.3\text{Hz}$, 1H),
 25 7.20(d, $J=5.7\text{Hz}$, 1H), 7.14(d, $J=5.7\text{Hz}$, 1H),
 7.11(dd, $J=2.7\text{Hz}$, 9.3Hz, 1H), 7.01(d, $J=2.7\text{Hz}$, 1H),
 6.82(d, $J=7.3\text{Hz}$, 1H), 6.78~6.72(m, 2H), 3.92(s, 3H), 3.80(s, 3H),
 3.43(m, 4H), 2.87(t, $J=4.4\text{Hz}$, 4H), 2.50~2.47(m, 2H),
 2.16~2.10(m, 4H), 2.06~1.98(m, 4H)
 30 Mass, m/e : 431(M^+), 416, 187(base), 121

Production Example 69

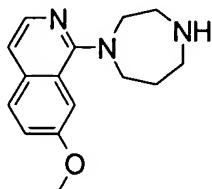
In the manner similar to Production Example 1,
 1-[4-(2,3-dihydrobenzo[1,4]dioxan-2-ylmethyl)piperazin-1-yl]-7-
 35 methoxyisoquinoline was obtained.



5 $^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.06(d, $J=5.7\text{Hz}$, 1H), 7.66(d, $J=9.0\text{Hz}$, 1H),
 7.39(d, $J=2.3\text{Hz}$, 1H), 7.22(d, $J=5.4\text{Hz}$, 1H),
 7.28(dd, $J=2.3\text{Hz}$, 8.8Hz, 1H), 6.89(dd, $J=4.6\text{Hz}$, 9.6Hz, 1H),
 6.84(dd, $J=3.4\text{Hz}$, 5.8Hz, 1H), 4.41~4.35(m, 2H),
 4.05(dd, $J=7.4\text{Hz}$, 11.2Hz, 1H), 3.94(s, 3H),
 10 3.41(t, $J=4.5\text{Hz}$, 4H), 2.92~2.85(m, 2H), 2.83~2.73(m, 4H)
 Mass, m/e : 391(M^+), 376, 282, 187(base), 174

Production Example 70

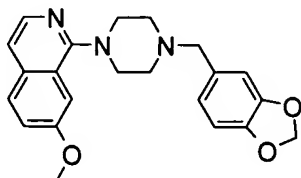
In the manner similar to Production Example 1,
 15 1-[1,4]diazepan-1-yl-7-methoxyisoquinoline was obtained.



20 $^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.02~7.99(m, 2H), 7.11~7.09(m, 2H),
 7.00(d, $J=2.3\text{Hz}$, 1H), 3.92(s, 3H), 3.76(t, $J=5.4\text{Hz}$, 2H),
 3.72(t, $J=5.8\text{Hz}$, 2H), 3.27(t, $J=5.4\text{Hz}$, 2H), 3.16(t, $J=5.7\text{Hz}$, 2H),
 2.75(br s, 1H), 2.00~1.95(m, 2H)
 25 Mass, m/e : 257(M^+), 242, 201, 187(base)

Production Example 71

In the manner similar to Production Example 1,
 1-(4-benzo[1,3]dioxol-5-ylmethylpiperazin-1-yl)-7-
 30 methoxyisoquinoline was obtained.



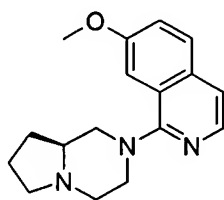
35

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.07(d, $J=5.8\text{Hz}$, 1H), 7.97(d, $J=9.3\text{Hz}$, 1H),
 7.13(d, $J=5.8\text{Hz}$, 1H), 7.09(dd, $J=2.7\text{Hz}$, 9.3Hz, 1H),
 7.00(d, $J=2.7\text{Hz}$, 1H), 6.91(s, 1H), 6.77(t, $J=7.2\text{Hz}$, 2H), 5.94(s, 2H),
 3.91(s, 3H), 3.53(s, 2H), 3.39(m, 4H), 2.69(t, $J=4.5\text{Hz}$, 4H)

5 Mass, m/e : 377(M^+), 187(base), 174, 135

Production Example 72

In the manner similar to Production Example 1,
 1-((8aS)-octahydropyrrolo[1,2-a]pyrazin-2-yl)-7-methoxyisoquinoline
 10 was obtained.



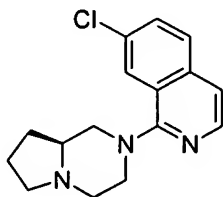
15

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.07(d, $J=5.4\text{Hz}$, 1H), 7.68(d, $J=8.9\text{Hz}$, 1H),
 7.40(d, $J=2.7\text{Hz}$, 1H), 7.29(dd, $J=2.3\text{Hz}$, 8.9Hz, 1H),
 7.21(d, $J=5.4\text{Hz}$, 1H), 3.94(s, 3H), 3.87~3.84(m, 1H),
 3.79~3.75(m, 2H), 3.22~3.16(m, 2H), 2.93~2.88(m, 1H),
 20 2.64~2.58(m, 1H), 2.40~2.38(m, 1H), 2.29(q, $J=8.5\text{Hz}$, 1H),
 1.94~1.76(m, 3H), 1.65~1.52(m, 1H)

Mass, m/e : 283(M^+), 96(base)

Production Example 73

25 In the manner similar to Production Example 1,
 7-chloro-1-((8aS)-octahydropyrrolo[1,2-a]pyrazin-2-yl)isoquinoline
 was obtained.



30

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.14(d, $J=5.8\text{Hz}$, 1H), 8.04(d, $J=2.3\text{Hz}$, 1H),
 35 7.68(d, $J=8.9\text{Hz}$, 1H), 7.55~7.52(m, 1H), 7.19(d, $J=5.4\text{Hz}$, 1H),

3.87~3.83(m,1H),3.78~3.73(m,1H),3.24~3.16(m,3H),
 2.93~2.87(m,1H),2.63~2.60(m,1H),2.38~2.25(m,2H),
 1.93~1.83(m,3H),1.63~1.51(m,1H)

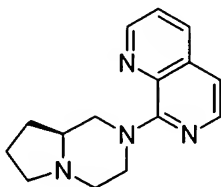
Mass,m/e:287(M⁺),96(base)

5

Production Example 74

In the manner similar to Production Example 1,
 8-((8aS)-octahydropyrrolo[1,2-a]pyrazin-2-yl)-1,7-naphthyridine was
 obtained.

10



15

¹H-NMR(CDCl₃)δ:8.83(dd,J=1.9Hz,4.2Hz,1H),
 8.13(d,J=5.4Hz,1H),8.01(dd,J=1.9Hz,8.5Hz,1H),
 7.48(dd,J=4.3Hz,8.5Hz,1H),7.04(d,J=5.4Hz,1H),
 4.96~4.90(m,2H),3.32~3.25(m,1H),3.19~3.15(m,2H),
 2.97~2.92(m,1H),2.62~2.56(m,1H),2.34~2.33(m,1H),
 2.25(q,J=8.9Hz,1H),1.96~1.85(m,2H),1.82~1.75(m,1H),
 1.56~1.50(m,1H)

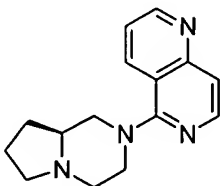
20

Mass,m/e:254(M⁺),96(base)

Production Example 75

In the manner similar to Production Example 1,
 5-((8aS)-octahydropyrrolo[1,2-a]pyrazin-2-yl)-1,6-naphthyridine was
 obtained.

30



¹H-NMR(CDCl₃)δ:8.98(dd,J=1.9Hz,4.2Hz,1H),
 8.40~8.37(m,1H),8.33(d,J=5.8Hz,1H),7.47~7.40(m,2H),
 3.93(td,J=2.3Hz,8.3Hz,1H),3.82(dd,J=2.7Hz,11.8Hz,1H),

35

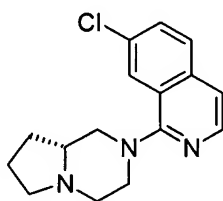
3.32~3.25(m,1H),3.21~3.16(m,2H),2.97~2.93(m,1H),
 2.59(dt,J=2.7Hz,11.2Hz,1H),2.37~2.25(m,2H),
 1.94~1.75(m,3H),1.55~1.50(m,1H)
 Mass,m/e:254(M⁺),96(base)

5

Production Example 76

In the manner similar to Production Example 1,
 7-chloro-1-((8aR)-octahydropyrrolo[1,2-a]pyrazin-2-yl)isoquinoline
 was obtained.

10



15

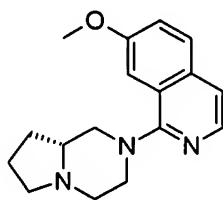
¹H-NMR(CDCl₃)δ:8.15(d,J=5.8Hz,1H),8.06(d,J=1.9Hz,1H),
 7.69(d,J=8.9Hz,1H),7.55(dd,J=1.9Hz,8.9Hz,1H),
 7.21(d,J=5.8Hz,1H),3.86(td,J=2.3Hz,11.6Hz,1H),
 3.80~3.75(m,1H),3.25~3.17(m,3H),2.94~2.88(m,1H),
 2.65~2.59(m,1H),2.39~2.34(m,1H),2.28(t,J=8.9Hz,1H),
 1.95~1.84(m,2H),1.84~1.75(m,1H),1.55~1.48(m,1H)
 Mass,m/e:287(M⁺),96(base)

20

Production Example 77

In the manner similar to Production Example 1,
 1-((8aR)-octahydropyrrolo[1,2-a]pyrazin-2-yl)-7-methoxyisoquinoline
 was obtained.

30



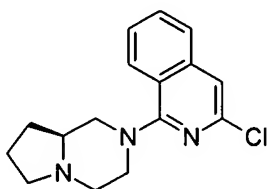
¹H-NMR(CDCl₃)δ:8.06(d,J=5.8Hz,1H),
 7.66(dd,J=3.4Hz,8.9Hz,1H),7.39(d,J=2.3Hz,1H),

35

7.27(dd, J=2.3Hz, 8.9Hz, 1H), 7.19(d, J=5.4Hz, 1H), 3.93(s, 3H),
 3.85(td, J=2.3Hz, 12.0Hz, 1H), 3.77~3.74(m, 1H),
 3.20~3.15(m, 3H), 2.89(t, J=10.8Hz, 1H), 2.60(t, J=11.2Hz, 1H),
 2.39~2.37(m, 1H), 2.32~2.25(m, 1H), 1.93~1.83(m, 2H),
 1.80~1.76(m, 1H), 1.59~1.51(m, 1H)
 Mass, m/e: 283(M⁺), 96(base)

Production Example 78

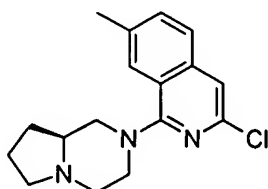
In the manner similar to Production Example 1,
 3-chloro-1-((8aS)-octahydropyrrolo[1,2-a]pyrazin-2-yl)isoquinoline
 was obtained.



¹H-NMR(CDCl₃) δ: 8.00(d, J=8.5Hz, 1H), 7.64(d, J=7.7Hz, 1H),
 7.60~7.56(m, 1H), 7.46~7.42(m, 1H), 7.22(s, 1H),
 3.99(td, J=2.3Hz, 12.3Hz, 1H), 3.93~3.89(m, 1H),
 3.24(dt, J=2.7Hz, 12.0Hz, 1H), 3.18~3.13(m, 2H),
 2.95~2.90(m, 1H), 2.61~2.23(m, 2H), 1.93~1.83(m, 1H),
 1.81~1.74(m, 2H), 1.53~1.47(m, 1H)
 Mass, m/e: 287(M⁺), 96(base)

Production Example 79

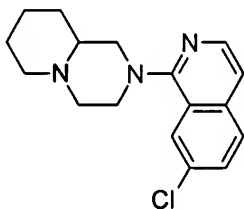
In the manner similar to Production Example 1,
 3-chloro-1-((8aS)-octahydropyrrolo[1,2-a]pyrazin-2-yl)-7-
 methylisoquinoline was obtained.



$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.55(d, $J=8.5\text{Hz}$, 1H),
 7.42(dd, $J=1.5\text{Hz}$, 8.5Hz, 1H), 7.19(s, 1H),
 3.95(td, $J=2.3\text{Hz}$, 12.3Hz, 1H), 3.90~3.86(m, 1H),
 3.25~3.13(m, 2H), 2.95~2.89(m, 1H), 2.62~2.57(m, 1H),
 2.51(s, 3H), 2.35~2.24(m, 2H), 1.91~1.83(m, 2H),
 1.79~1.76(m, 1H), 1.56~1.51(m, 1H)
 Mass, m/e : 301(M^+), 96(base)

Production Example 80

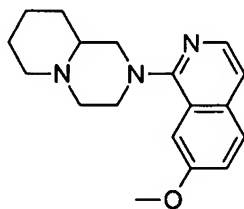
In the manner similar to Production Example 1,
 7-chloro-1-octahydropyrido[1,2-a]pyrazin-2-ylisoquinoline was
 obtained.



$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.15(d, $J=5.8\text{Hz}$, 1H), 8.05(d, $J=1.9\text{Hz}$, 1H),
 7.69(d, $J=8.9\text{Hz}$, 1H), 7.55(dd, $J=1.9\text{Hz}$, 8.9Hz, 1H),
 7.21(d, $J=5.8\text{Hz}$, 1H), 3.72(qd, $J=2.7\text{Hz}$, 12.3Hz, 1H),
 3.56(td, $J=2.7\text{Hz}$, 12.3Hz, 1H), 3.23(dt, $J=2.7\text{Hz}$, 12.3Hz, 1H),
 2.97~2.84(m, 3H), 2.63(dt, $J=2.7\text{Hz}$, 11.6Hz, 1H),
 2.33~2.16(m, 2H), 1.87~1.78(m, 1H), 1.75~1.57(m, 3H),
 1.45~1.28(m, 2H)
 Mass, m/e : 301(M^+), 110(base)

Production Example 81

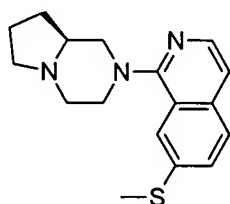
In the manner similar to Production Example 1,
 7-methoxy-1-octahydropyrido[1,2-a]pyrazin-2-ylisoquinoline was
 obtained.



$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.07(d, $J=5.4\text{Hz}$, 1H), 7.67(d, $J=8.9\text{Hz}$, 1H),
 7.40(d, $J=2.7\text{Hz}$, 1H), 7.28(dd, $J=2.7\text{Hz}$, 8.9Hz, 1H),
 7.20(d, $J=5.8\text{Hz}$, 1H), 3.94(s, 3H), 3.72(qd, $J=2.7\text{Hz}$, 12.3Hz, 1H),
 3.57(td, $J=2.7\text{Hz}$, 12.3Hz, 1H), 3.26~3.16(m, 1H),
 2.98~2.84(m, 3H), 2.63(dt, $J=2.7\text{Hz}$, 11.6Hz, 1H),
 2.35~2.25(m, 1H), 2.25~2.15(m, 1H), 1.84~1.54(m, 4H),
 1.42~1.32(m, 2H)
 Mass, m/e : 297(M^+), 110(base)

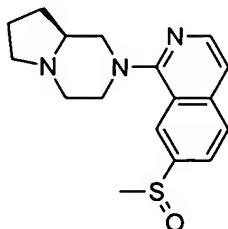
Production Example 82

In the manner similar to Production Example 1,
 7-methylsulfanyl-1-(S)-octahydropyrido[1,2-a]pyran-2-ylisoquinoline
 was obtained.



$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.10(d, $J=5.8\text{Hz}$, 1H), 7.85(d, $J=1.9\text{Hz}$, 1H),
 7.65(d, $J=8.5\text{Hz}$, 1H), 7.50(dd, $J=1.9\text{Hz}$, 8.5Hz, 1H),
 7.18(d, $J=5.8\text{Hz}$, 1H), 3.91~3.84(m, 1H), 3.82~3.75(m, 1H),
 3.25~3.15(m, 3H), 2.94~2.85(m, 1H), 2.59(s, 3H), 2.43~2.24(m, 2H),
 1.97~1.73(m, 3H), 1.66~1.47(m, 2H)
 Mass, m/e : 299(M^+), 96(base)

Production Example 83

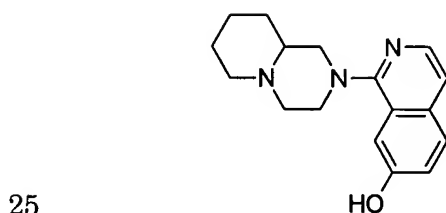


First, in the manner similar to Production Example 1, 285 mg

of 7-methylsulfanyl-1-(S)-octahydropyrido[1,2-a]pyran-2-ylisoquinoline was obtained, to which 1 ml of 30% aqueous hydrogen peroxide and 0.5 ml of acetic acid were added, stirred at room temperature for 15 minutes, rendered alkaline with ammonia water,
 5 extracted with dichloromethane and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, the residue was purified on silica gel column chromatography (methanol : dichloromethane = 1:4) to provide 235 mg (78%) of 7-methanesulfinyl-1-(S)-octahydropyrido[1,2-a]pyran-
 10 2-ylisoquinoline.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.43~8.40(m, 1H), 8.23(d, J=5.8Hz, 1H), 7.89(d, J=8.5Hz, 1H), 7.77~7.73(m, 1H), 7.28~7.25(m, 1H), 3.94(d, J=12.0Hz, 1H), 3.89~3.81(m, 1H), 3.33~3.23(m, 1H),
 15 3.23~3.14(m, 2H), 3.02~2.91(m, 1H), 2.79(d, J=1.5Hz, 3H), 2.70~2.60(m, 1H), 2.46~2.25(m, 2H), 1.97~1.75(m, 3H), 1.62~1.46(m, 1H)
 Mass, m/e: 315(M^+), 96(base)

20 Production Example 84



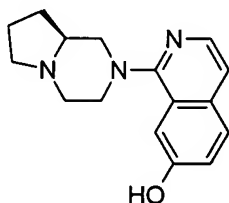
First, in the manner similar to Production Example 1, 610 mg of 7-methoxy-1-octahydropyrido[1,2-a]pyrazin-2-ylisoquinoline was obtained, to which 8 ml of 47% aqueous hydrobromic acid was added
 30 and heated under reflux for 2 hours. After cooling, the solution was neutralized with 5N aqueous sodium hydroxide, followed by extraction with chloroform, drying over anhydrous magnesium sulfate, and removal of the solvent by distillation under reduced pressure. The residue was purified on silica gel column
 35 chromatography (saturated aqueous ammonia : methanol :

chloroform = 0.5 : 5 : 45) to provide 500 mg (86%) of 7-hydroxy-1-octahydropyrido[1,2-a]pyrazin-2-ylisoquinoline.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.03(dd, $J=1.2\text{Hz}, 5.8\text{Hz}$, 1H),
 7.67(d, $J=8.9\text{Hz}$, 1H), 7.41(d, $J=2.3\text{Hz}$, 1H), 7.27~7.21(m, 1H),
 7.20(d, $J=5.8\text{Hz}$, 1H), 3.71~3.63(m, 1H), 3.58~3.51(m, 1H),
 3.27~3.17(m, 1H), 2.95~2.83(m, 3H), 2.60~2.50(m, 1H),
 2.31~2.07(m, 2H), 1.82~1.54(m, 4H), 1.39~1.26(m, 2H).
 Mass, m/e : 283(M^+), 110(base)

Production Example 85

In the manner similar to Production Example 84, 1-(S)-octahydropyrido[1,2-a]pyran-2-yl-7-hydroxyisoquinoline was obtained.



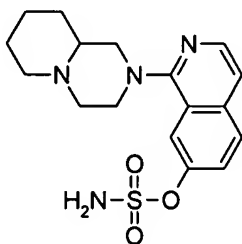
$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.02(d, $J=5.4\text{Hz}$, 1H), 7.68(d, $J=8.9\text{Hz}$, 1H),
 7.42(d, $J=2.3\text{Hz}$, 1H), 7.29~7.25(m, 1H), 7.23(d, $J=5.4\text{Hz}$, 1H),
 3.71~3.58(m, 2H), 3.32~3.23(m, 1H), 3.21~3.13(m, 2H),
 3.01~2.85(m, 3H), 2.55~2.46(m, 1H), 1.98~1.79(m, 3H),
 1.59~1.49(m, 1H)
 Mass, m/e : 269(M^+), 96(base)

Production Example 86

In 3 ml of N-methylpyrrolidone, 105 mg of 7-hydroxy-1-octahydropyrido[1,2-a]pyrazin-2-ylisoquinoline as synthesized in Production Example 84 was dissolved, and to the solution 1.00 g of sulfamoyl chloride was added, followed by an hour's stirring at room temperature. The solution was neutralized with saturated aqueous sodium hydrogencarbonate solution, extracted with chloroform, dried

over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified on silica gel column chromatography (25% aqueous ammonia : methanol : chloroform = 1:10:90) to provide 85 mg (75%) of

5 1-octahydropyrido[1,2-a]pyrazin-2-yl-7-sulfamoylisoquinoline.



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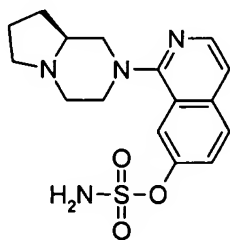
$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.05(d, $J=5.8\text{Hz}$, 1H), 7.97(d, $J=2.7\text{Hz}$, 1H),
7.75(d, $J=8.9\text{Hz}$, 1H), 7.57(dd, $J=2.7\text{Hz}$, 8.9Hz, 1H),
7.14(d, $J=5.8\text{Hz}$, 1H), 3.62~3.49(m, 2H),
3.05(dt, $J=2.7\text{Hz}$, 12.3Hz, 1H), 2.94~2.72(m, 3H),
2.54(dt, $J=3.1\text{Hz}$, 11.6Hz, 1H), 2.27(t, $J=10.8\text{Hz}$, 1H),
2.21~2.12(m, 1H), 1.83~1.54(m, 4H), 1.43~1.21(m, 2H)
Mass, m/e : 362(M^+), 110(base)

20

Production Example 87

In the manner similar to Production Example 86,
1-(S)-octahydropyrido[1,2-a]pyran-2-yl-7-sulfamoylisoquinoline was
obtained.

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$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.08(d, $J=5.8\text{Hz}$, 1H), 7.98(d, $J=2.3\text{Hz}$, 1H),
7.77(d, $J=8.9\text{Hz}$, 1H), 7.57(dd, $J=2.3\text{Hz}$, 8.9Hz, 1H),
7.17(d, $J=5.8\text{Hz}$, 1H), 3.85~3.78(m, 1H), 3.73~3.65(m, 1H),
3.18~3.05(m, 3H), 2.86~2.78(m, 1H), 2.63~2.54(m, 1H),
2.43~2.24(m, 2H), 1.95~1.74(m, 3H), 1.53~1.41(m, 1H)

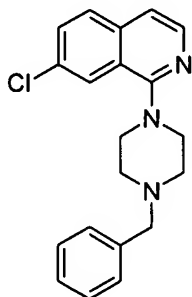
Mass, m/e: 348(M⁺), 96(base)

Production Example 88

Step 1: Synthesis of 1-(4-benzylpiperazin-1-yl)-7-chloroisoquinoline

5

10



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A mixture of 3.96 g 1,7-dichloroisoquinoline and 10.50 g of benzylpiperazine was stirred at 150°C for 3 hours. To the residue water was added, followed by extraction with chloroform, washing with saturated aqueous sodium hydrogencarbonate solution and drying over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, the residue was purified on silica gel column chromatography (ethyl acetate) to provide 4.78 g (71%) of 1-(4-benzylpiperazin-1-yl)-7-chloroisoquinoline.

20

¹H-NMR(CDCl₃) δ: 8.14(d, J=5.4Hz, 1H), 8.04(d, J=1.9Hz, 1H), 7.68(d, J=8.5Hz, 1H), 7.53(dd, J=2.3Hz, 8.8Hz, 1H), 7.39~7.23(m, 5H), 7.20(d, J=5.8Hz, 1H), 3.64(s, 2H), 3.41(t, J=5.6Hz, 4H), 2.73(t, J=4.8Hz, 4H)

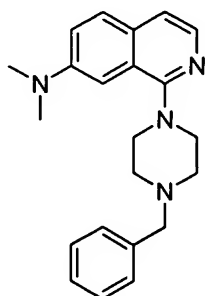
25

Mass, m/e: 337(M⁺), 191, 159, 91(base)

Step 2: Synthesis of 1-(4-benzylpiperazin-1-yl)-7-dimethylaminoisoquinoline

30

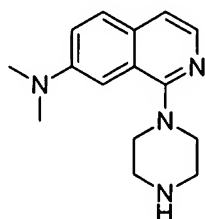
35



After dissolving 1.01 g of 1-(4-benzylpiperazin-1-yl)-7-chloroisoquinoline as synthesized in above Step 1 in 30 ml of tetrahydrofuran, 20 mg of palladium acetate, 48 mg of 2-(di-tert-butylphosphino)biphenyl, 450 mg of sodium-tert-butoxide and 5 ml of 2.0 M dimethylamine-tetrahydrofuran solution were added to the solution and sealed in a tube. This mixture was stirred at 80°C for 16 hours. Removing the insoluble matter by filtration, the solvent was distilled off under reduced pressure and the residue was purified on silica gel column chromatography (methanol : chloroform = 1:19) to provide 261 mg (25%) of 1-(4-benzylpiperazin-1-yl)-7-dimethylaminoisoquinoline.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.94(d, J=5.7Hz, 1H), 7.63(d, J=9.0Hz, 1H), 7.45~7.20(m, 6H), 7.18(d, J=5.4Hz, 1H), 7.12(d, J=2.3Hz, 1H), 3.69(s, 2H), 3.49(t, J=4.8Hz, 4H), 3.06(s, 6H), 2.77(t, J=5.0Hz, 4H)
Mass, m/e: 346(M^+), 330, 200(base), 187, 91

Step 3: Synthesis of 7-dimethylamino-1-piperazin-1-ylisoquinoline



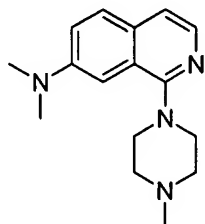
After dissolving 250 mg of 1-(4-benzylpiperazin-1-yl)-7-dimethylaminoisoquinoline as synthesized in above Step 2 in 20 ml of ethanol, 50 mg of 10% palladium-on carbon was added to the solution. This mixture was stirred for 16 hours at room temperature in hydrogen atmosphere. The insoluble matter was removed by filtration and the solvent was distilled off under reduced pressure. The residue was purified on silica gel column chromatography (methanol : chloroform = 1:9) to provide 46 mg (25%) of 7-dimethylamino-1-piperazin-1-ylisoquinoline.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.95(d, $J=5.4\text{Hz}$, 1H), 7.64(d, $J=8.9\text{Hz}$, 1H),
 7.27(dd, $J=2.3\text{Hz}$, 8.9Hz, 1H), 7.16(d, $J=5.4\text{Hz}$, 1H),
 7.12(d, $J=2.3\text{Hz}$, 1H), 3.39(t, $J=5.0\text{Hz}$, 4H), 3.19(t, $J=5.0\text{Hz}$, 4H),
 3.07(s, 6H)

5 Mass, m/e : 256(M^+), 200, 187(base)

Production Example 89

The compound as obtained in above Production Example
 88 was methylated according to accepted practice to provide
 10 7-dimethylamino-1-(4-methylpiperazin-1-yl)isoquinoline.

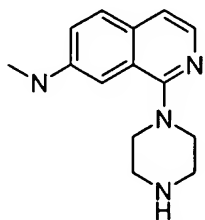


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$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.95(d, $J=5.7\text{Hz}$, 1H), 7.63(d, $J=9.0\text{Hz}$, 1H),
 7.32(dd, $J=2.8\text{Hz}$, 9.0Hz, 1H), 7.21(d, $J=5.4\text{Hz}$, 1H),
 7.12(d, $J=2.8\text{Hz}$, 1H), 3.45(t, $J=5.0\text{Hz}$, 4H), 3.07(s, 6H),
 20 2.71(t, $J=5.0\text{Hz}$, 4H), 2.42(s, 3H)
 Mass, m/e : 270(M^+), 200, 187(base)

Production Example 90

In the manner similar to Production Example 88,
 25 7-methylamino-1-piperazin-1-ylisoquinoline was obtained.

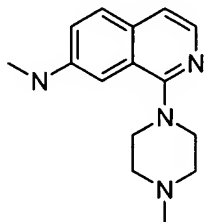


30

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.93(d, $J=5.8\text{Hz}$, 1H), 7.57(d, $J=8.9\text{Hz}$, 1H),
 7.17(d, $J=5.4\text{Hz}$, 1H), 7.01(dd, $J=1.3\text{Hz}$, 8.9Hz, 1H),
 6.90(d, $J=1.9\text{Hz}$, 1H), 3.56(t, $J=5.0\text{Hz}$, 4H), 3.33(t, $J=5.0\text{Hz}$, 4H),
 2.94(s, 3H)
 35 Mass, m/e : 242(M^+), 198, 186, 173(base)

Production Example 91

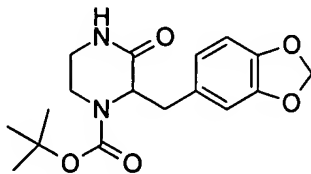
In the manner similar to Production Example 89,
7-methylamino-1-(4-methylpiperazin-1-yl)isoquinoline was obtained.



$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.94(d, $J=5.7\text{Hz}$, 1H), 7.55(d, $J=9.5\text{Hz}$, 1H),
7.21(d, $J=9.2\text{Hz}$, 1H), 7.07(dd, $J=2.6\text{Hz}$, 5.1Hz, 1H),
6.97(d, $J=2.0\text{Hz}$, 1H), 3.44(t, $J=4.8\text{Hz}$, 4H), 2.95(s, 3H),
2.72(t, $J=5.0\text{Hz}$, 4H), 2.42(s, 3H)
Mass, m/e : 256(M^+), 186(base), 173, 157

Production Example 92

Step 1: Synthesis of 2-benzo[1,3]dioxol-5-ylmethyl-1-tert-
butoxycarbonyl-3-oxopiperazine



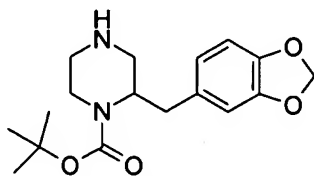
Under argon atmosphere, 17.5 ml of 1.58M n-butyl
lithium-n-hexane solution was dropped into a mixture of 25 ml of
tetrahydrofuran and 2.78 g of diisopropylamine under cooling ice,
followed by 30 minutes' stirring under the same condition.
Thereafter a solution of 2.50 g of 1-tert-butoxycarbonyl-3-
oxopiperazine (which was prepared by following Tetrahedron Lett.,
1980, 21, 3019 – 3020) in 60 ml of tetrahydrofuran was added by
dropping under cooling with ice, followed by 3 hours' stirring under
the same condition, further dropping of a solution of 2.30 g of

5-chloromethyl-benzo[1,3]dioxole in 20 ml of tetrahydrofuran under cooling with ice, and an hour's stirring under the same condition. The solution was warmed to room temperature and stirred for 18 hours. After addition of saturated aqueous ammonium chloride solution, the solution was extracted with ethyl acetate, dried over anhydrous magnesium sulfate and the solvent was distilled therefrom under reduced pressure. The residue was purified on silica gel column chromatography (ethyl acetate) to provide 2.84 g (68%) of 2-benzo[1,3]dioxol-5-ylmethyl-1-tert-butoxycarbonyl-3-oxopiperazine.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 6.67(s, 1H), 6.65(d, $J=1.3\text{Hz}$, 2H), 5.90(s, 2H), 4.52~4.43(m, 1H), 4.12(d, $J=7.2\text{Hz}$, 2H), 3.23(t, $J=5.1\text{Hz}$, 2H), 2.57(t, $J=5.8\text{Hz}$, 2H), 1.45(s, 9H)
Mass, m/e : 334(M^+), 278, 144, 57(base)

Step 2: Synthesis of 2-benzo[1,3]dioxol-5-ylmethyl-1-tert-butoxycarbonylpiperazine

20



Dissolving 2.00 g of 2-benzo[1,3]dioxol-5-ylmethyl-1-tert-butoxycarbonyl-3-oxopiperazine as synthesized in the above step in 50 ml of tetrahydrofuran, 1.00 g of lithium aluminium hydride was added to the solution which then was heated under reflux for 16 hours. To the solution 10% aqueous potassium hydroxide solution was added, the insoluble matter was filtered off, extracted with ethyl acetate, the extract was dried over anhydrous magnesium sulfate and the solvent was distilled off under reduced pressure. The residue was purified on silica gel column chromatography (methanol : chloroform = 1:19) to provide 1.27 g (66%) of 2-benzo[1,3]dioxol-5-ylmethyl-1-tert-butoxycarbonylpiperazine.

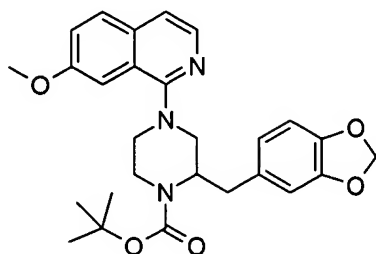
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$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 6.68(s, 1H), 6.65(d, $J=0.5\text{Hz}$, 2H), 5.90(s, 2H),
 4.02~3.87(m, 3H), 3.78~3.54(m, 2H), 2.96~2.77(m, 2H),
 2.65~2.51(m, 2H), 1.45(s, 9H)
 Mass, m/e : 320(M^+), 219, 57(base)

5

Step 3: Synthesis of 1-(2-benzo[1,3]dioxol-5-ylmethyl-1-tert-
butoxycarbonylpiperazin-4-yl)-7-methoxyisoquinoline

10

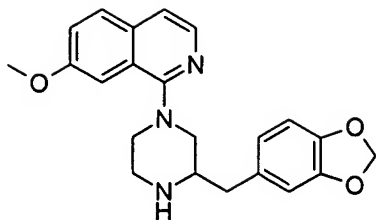


15

A mixture of 320 mg of 2-benzo[1,3]dioxol-5-ylmethyl-1-tert-butoxycarbonylpiperazine as synthesized in the above step, 200 mg of 1-chloro-7-methoxyisoquinoline and 100 mg of triethylamine was stirred in 2 ml of ethylene glycol at 150°C for 18 hours. After
 20 addition of water, the solution was extracted with ethyl acetate, dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified on silica gel column chromatography (ethyl acetate : n-hexane = 1:1) to provide
 210 mg (44%) of 1-(2-benzo[1,3]dioxol-5-ylmethyl-1-tert-
 25 butoxycarbonylpiperazin-4-yl)-7-methoxyisoquinoline.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.05(d, $J=5.5\text{Hz}$, 1H), 7.64(d, $J=9.1\text{Hz}$, 1H),
 7.26(dd, $J=2.1\text{Hz}$, 9.1Hz, 1H), 7.22(d, $J=5.4\text{Hz}$, 1H),
 7.08(d, $J=2.1\text{Hz}$, 1H), 6.92(s, 1H), 6.79(d, $J=1.3\text{Hz}$, 1H),
 30 5.94(s, 2H), 3.93(s, 3H), 3.33~3.26(m, 2H), 3.21~3.14(m, 2H),
 2.80~2.66(m, 3H), 1.45(s, 9H)
 Mass, m/e : 477(M^+), 342(base), 187, 135

Step 4: Synthesis of 1-(3-benzo[1,3]dioxol-5-ylmethylpiperazin-1-yl)-
 35 7-methoxyisoquinoline

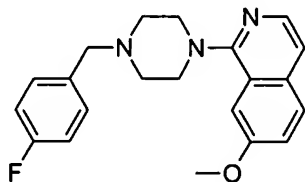


5

In 10 ml of 4N hydrochloric acid-dioxane solution, 150 mg of 1-(2-benzo[1,3]dioxol-5-ylmethyl-1-tert-butoxycarbonylpiperazin-4-yl)-7-methoxyisoquinoline as synthesized in the above step was added and stirred for 18 hours. The solution was neutralized with saturated aqueous sodium hydrogencarbonate solution, extracted with ethyl acetate, dried over anhydrous magnesium sulfate and the solvent was distilled off under reduced pressure. The residue was purified on silica gel column chromatography (methanol : chloroform = 1:9) to provide 69 mg (58%) of 1-(3-benzo[1,3]dioxol-5-ylmethylpiperazin-1-yl)-7-methoxyisoquinoline.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.07(d, $J=5.5\text{Hz}$, 1H), 7.66(d, $J=9.2\text{Hz}$, 1H), 7.33~7.30(m, 1H), 7.25~7.18(m, 2H), 6.74(s, 1H), 6.72(d, $J=0.8\text{Hz}$, 1H), 5.93(s, 2H), 3.84(s, 3H), 3.66~3.59(m, 2H), 3.30~3.18(m, 2H), 3.15~3.10(m, 2H), 2.80~2.64(m, 3H)
Mass, m/e : 377(M^+), 242(base), 187, 135

25 Production Example 93



30

Into 10 ml of acetone, 50 mg of 7-methoxy-1-piperazin-1-ylisoquinoline, 100 mg of 4-fluorobenzyl bromide and 100 mg of triethylamine were added and heated under reflux for 5 hours. Distilling the solvent off under reduced pressure, the residue was purified on silica gel column chromatography (methanol : chloroform

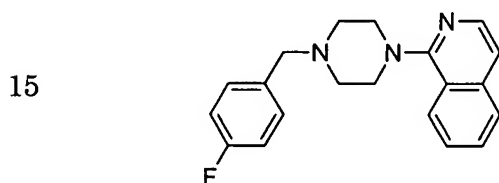
35

= 1:19) to provide 52 mg (79%) of 1-[4-(4-fluorobenzyl)piperazin-1-yl]-7-methoxyisoquinoline.

¹H-NMR(CDCl₃)δ: 8.07(d, J=5.5Hz, 1H), 7.68(d, J=9.2Hz, 1H),
 5 7.41~7.32(m, 3H), 7.30~7.26(m, 1H), 7.21(d, J=5.5Hz, 1H),
 7.06~6.99(m, 2H), 3.93(s, 3H), 3.61(s, 2H), 3.45~3.35(m, 4H),
 2.77~2.67(m, 4H)
 Mass, m/e: 351(M⁺), 187(base)

10 Production Example 94

In the manner similar to Production Example 93, 1-[4-(4-fluorobenzyl)piperazin-1-yl]isoquinoline was obtained.

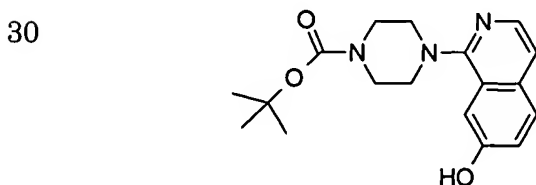


¹H-NMR(CDCl₃)δ: 8.14(d, J=5.8Hz, 1H), 8.08(d, J=8.5Hz, 1H),
 20 7.74(d, J=8.1Hz, 1H), 7.59(ddd, J=1.2Hz, 6.9Hz, 8.1Hz, 1H),
 7.49(ddd, 1.2Hz, 6.9Hz, 8.5Hz, 1H), 7.38~7.32(m, 2H),
 7.23(d, J=5.8Hz, 1H), 7.06~6.99(m, 2H), 3.61(s, 2H),
 3.47~3.40(m, 4H), 2.75~2.68(m, 4H)
 Mass, m/e: 321(M⁺), 157(base)

25

Production Example 95

Step 1: Synthesis of 1-(4-tert-butoxycarbonylpiperazin-1-yl)-7-hydroxyisoquinoline



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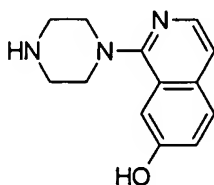
A mixture of 4.00 g of 7-methoxy-1-piperazin-1-

ylisoquinoline and 40 ml of 47% aqueous hydrobromic acid was heated under reflux for 2 hours. After cooling, the residue was rendered alkaline with 5N aqueous sodium hydroxide solution, followed by addition of 30 ml of 1,4-dioxane and 3.94 g of
 5 di-tert-butylidicarbonate and an hour's stirring at room temperature. The solution was extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and the solvent was distilled off under reduced pressure. The residue was purified on silica gel column chromatography (methanol : chloroform = 1:19) to
 10 provide 4.63 g (85%) of 1-(4-tert-butoxycarbonylpiperazin-1-yl)-7-hydroxyisoquinoline.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.03(d, J=5.5Hz, 1H), 7.70(d, J=8.8Hz, 1H),
 7.43(d, J=2.6Hz, 1H), 7.30~7.23(m, 2H), 3.72~3.64(m, 4H),
 15 3.34~3.26(m, 4H), 1.51(s, 9H)
 Mass, m/e: 329(M^+), 173(base)

Step 2: Synthesis of 7-hydroxy-1-piperazin-1-ylisoquinoline hydrochloride

20



25

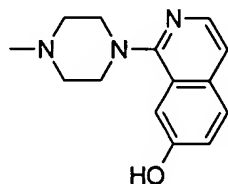
A mixture of 70 mg of 1-(4-tert-butoxycarbonylpiperazin-1-yl)-7-hydroxyisoquinoline as synthesized in the above step and 3 ml of 4N hydrochloric acid-ethyl acetate solution was stirred for an hour at room temperature. So formed crystalline product was recovered by
 30 filtration and washed with ethyl acetate to provide 43 mg (yield: 78%) of 7-hydroxy-1-piperazin-1-ylisoquinoline hydrochloride.

$^1\text{H-NMR}(\text{CD}_3\text{OD})\delta$: 8.02(d, J=8.5Hz, 1H), 7.78(d, J=6.6Hz, 1H),
 7.72(d, J=6.6Hz, 1H), 7.64~7.56(m, 2H), 4.06~3.98(m, 4H),
 35 3.68~3.59(m, 4H)

Mass, m/e: 229(M⁺), 173(base)

Production Example 96

5

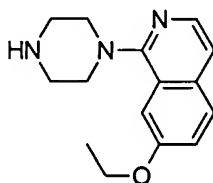


A mixture of 795 mg of 7-methoxy-(4-methylpiperazin-1-yl)-
 10 isoquinoline and 8 ml of 47% aqueous hydrobromic acid solution was
 heated under reflux for 2.5 hours. After cooling, the solution was
 neutralized with 20% aqueous sodium hydroxide solution, extracted
 with chloroform, dried over anhydrous magnesium sulfate and the
 solvent was distilled off under reduced pressure. The residue was
 15 purified on silica gel column chromatography (saturated ammonia
 water : methanol : chloroform = 1:10:90) to provide 673 mg (80%) of
 7-hydroxy-1-(4-methylpiperazin-1-yl)isoquinoline.

¹H-NMR(CDCl₃) δ: 8.01(d, J=5.8Hz, 1H), 7.66(d, J=8.5Hz, 1H),
 20 7.36(d, J=2.7Hz, 1H), 7.26~7.19(m, 2H), 3.48~3.35(m, 4H),
 2.70~2.55(m, 4H), 2.33(s, 3H)
 Mass, m/e: 243(M⁺), 173(base)

Production Example 97

25



30

To a solution of 105mg of 1-(4-tert-butoxycarbonylpiperazin-1-
 yl)-7-hydroxyisoquinoline in 10 ml of acetone, 93 mg of potassium
 carbonate and 55 mg of ethyl iodide were added and heated under
 reflux for 2 hours. Further adding 55 mg of ethyl iodide, the
 35 solution was heated under reflux for 2 hours, followed by addition of

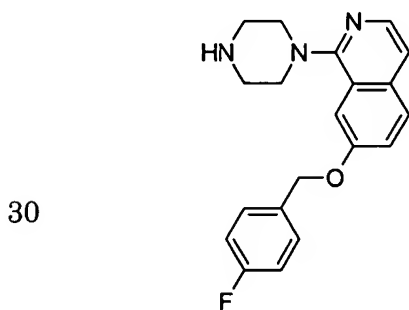
48 mg of potassium carbonate and 55 mg of ethyl iodide, and an overnight's refluxing. Cooling the system off, the residue was extracted with ethyl acetate after addition of water, washed with saturated brine, dried over anhydrous magnesium sulfate and the solvent was distilled off under reduced pressure. The residue was purified on silica gel column chromatography (ethyl acetate : n-hexane = 1:4) to provide 102 mg (90%) of 1-(4-tert-butoxycarbonylpiperazin-1-yl)-7-ethoxyisoquinoline.

Then the product was stirred in 3 ml of 4N hydrochloric acid-dioxane solution at room temperature for 30 minutes. The solution was rendered alkaline with 10% aqueous sodium hydroxide solution, extracted with ethyl acetate and the solvent was distilled off under reduced pressure. The residue was purified on silica gel column chromatography (methanol : chloroform = 1:4) to provide 67 mg (93%) of 7-ethoxy-1-piperazin-1-ylisoquinoline.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.07(d, J=5.8Hz, 1H), 7.67(d, J=8.9Hz, 1H), 7.40(d, J=2.3Hz, 1H), 7.28(dd, J=2.3Hz, 8.9Hz, 1H), 7.22(d, J=5.8Hz, 1H), 4.17(q, J=6.9Hz, 2H), 3.38~3.32(m, 4H), 3.20~3.14(m, 4H), 1.51(t, J=6.9Hz, 3H)
Mass, m/e: 257(M^+), 188(base)

Production Example 98

In the manner similar to Production Example 97, 7-(4-fluorobenzyloxy)-1-piperazin-1-ylisoquinoline was obtained.



$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.08(d, J=5.8Hz, 1H), 7.70(d, J=8.8Hz, 1H), 7.49~7.42(m, 2H), 7.41~7.38(m, 1H), 7.38~7.33(m, 1H), 7.22(d, J=5.8Hz, 1H), 7.12~7.06(m, 2H), 5.20(s, 2H),

35

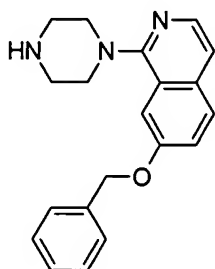
3.29~3.22(m,4H),3.13~3.06(m,4H)

Mass,m/e:337(M⁺),109(base)

Production Example 99

5 In the manner similar to Production Example 97,
7-benzyloxy-1-piperazin-1-ylisoquinoline was obtained.

10



15

¹H-NMR(CDCl₃)δ:8.06(d,J=5.8Hz,1H),7.69(d,J=8.9Hz,1H),

7.50~7.29(m,7H),7.21(d,J=5.8Hz,1H),5.25(s,2H),

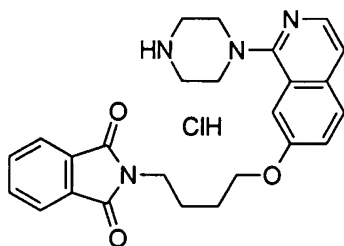
3.24~3.18(m,4H),3.08~3.02(m,4H)

Mass,m/e:319(M⁺),91(base)

Production Example 100

20 In the manner similar to Production Example 97,
7-[4-(1,3-dioxo-1,3-dihydroisindol-2-yl)butoxy]-1-piperazin-1-ylisoquinoline hydrochloride was obtained.

25



30

¹H-NMR(DMSO-d₆)δ:7.97~7.91(m,2H),7.89~7.80(m,4H),

7.57~7.48(m,2H),7.38(d,J=2.3Hz,1H),4.25~4.16(m,4H),

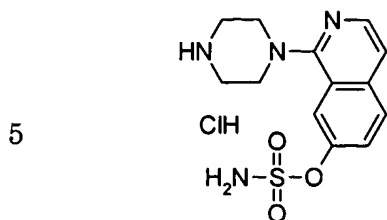
3.79~3.63(m,8H),1.87~1.77(m,4H)

Mass,m/e:430(M⁺),160(base)

Production Example 101

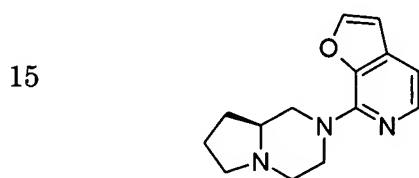
35 In the manner similar to Production Example 97,

7-sulfamoyloxy-1-piperazin-1-isoquinoline hydrochloride was obtained.



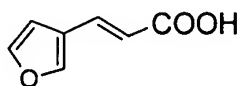
¹H-NMR(DMSO-d₆)δ:8.19~8.11(m,3H),8.07(d,J=8.9Hz,1H),
 7.98(d,J=2.3Hz,1H),7.69(dd,J=2.3Hz,8.9Hz,1H),
 10 7.57(d,J=5.8Hz,1H),3.65~3.57(m,4H),3.40~3.31(m,4H)

Production Example 102



Step 102-A

20



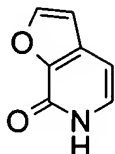
To 12 ml of pyridine, 10.0 g of 3-furaldehyde and 15.0 g of
 25 malonic acid were added, followed by heating under stirring at 80°C –
 90°C for 2 hours. The solution was poured into ice water, rendered
 weakly acidic with 1N hydrochloric acid. The precipitated crystals
 were recovered by filtration, dissolved in ethyl acetate and washed
 with 1N hydrochloric acid. The organic layer was dried over
 30 anhydrous magnesium sulfate and concentrated. The residue was
 recrystallized from ethyl acetate-n-hexane to provide 11.78 g (82%) of
 3-furan-3-ylallylic acid.

¹H-NMR(CDCl₃):7.70~7.67(m,2H),7.45(s,1H),
 35 6.62~6.61(m,1H),6.16(d,J=15.8Hz,1H)

Mass, m/e: 138 (M^+ , base)

Step 102-B

5



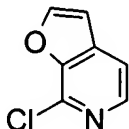
In 50 ml of acetone, 5.0 g of 3-furan-3-ylallylic acid as obtained in the above step 102-A and 4.3 g of triethylamine were dissolved, and to the solution 5.2 g of ethyl chlorocarbonate was dropped under cooling with ice, consuming 10 minutes, followed by 30 minutes' stirring under cooling with ice. Then an aqueous solution of sodium azide (formed by dissolving 3.5 g of sodium azide in 15 ml of purified water) was dropped, followed by another hour's stirring under cooling with ice. After addition of 150 ml of ice water, the solution was extracted with benzene, dried over anhydrous magnesium sulfate and concentrated to about 20 ml under reduced pressure, while maintaining the liquid temperature at not higher than 30°C. This solution was dropped into 40 ml of diphenylmethane and 7 ml of tributylamine which had been heated to 220°C over 1.5 hours while distilling the benzene off to maintain the temperature of 220°C. After termination of the dropping, the liquid was cooled, to which n-hexane was added. Whereupon precipitated crystals were recovered by filtration, washed with ethyl acetate and dried to provide 3.15 g (64%) of 6H-furo[2,3-c]pyridin-7-one.

$^1\text{H-NMR}$ (DMSO- d_6): 11.50(br s, 1H), 8.07(d, $J=1.9\text{Hz}$, 1H), 6.86(d, $J=1.9\text{Hz}$, 1H), 6.50(d, $J=6.9\text{Hz}$, 1H)

Mass, m/e: 135 (M^+ , base)

30

Step 102-C

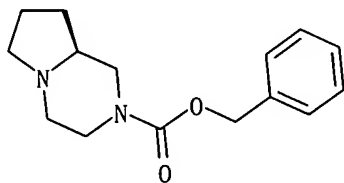


35

In 16.0 g of phosphorus oxychloride, 3.1 g of 6H-furo[2,3-c]-pyridin-7-one as obtained in above Step 102-B was heated under reflux for 1.5 hours. The solution was poured into ice, neutralized with saturated aqueous sodium hydrogencarbonate solution and
 5 extracted with chloroform. The extract was dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified on silica gel column chromatography (n-hexane : ethyl acetate = 1:1) to provide 2.36 g (67%) of 7-chlorofuro[2,3-c]pyridine.

10

$^1\text{H-NMR}(\text{CDCl}_3)$: 8.19(d, J=5.4Hz, 1H), 7.81(d, J=1.9Hz, 1H),
 7.49(d, J=5.4Hz, 1H), 6.87(d, J=2.3Hz, 1H)
 Mass, m/e: 153(M^+ , base)

15 Step 102-D

20

In 150 ml of tetrahydrofuran, 12.5 g of N-benzyloxycarbonyl-L-proline and 8.9 g of carbonyldiimidazole were dissolved and stirred for 30 minutes. Then 6.9 g of glycine methyl ester hydrochloride
 25 and 5.6 g of triethylamine were added to the solution and stirred for an overnight at room temperature. The solution was concentrated, and ethyl acetate was added, followed by washing with saturated aqueous sodium hydrogencarbonate solution, 10% aqueous citric acid and saturated brine, drying over anhydrous magnesium sulfate and
 30 concentration. The residue was dissolved in 100 ml of methanol, to which solution 2.0 g of 10% palladium-on-carbon was added and stirred for an overnight in gaseous hydrogen current. Filtering the catalyst off, the filtrate was concentrated. This residue was dissolved in 100 ml of methanol and following addition of
 35 triethylamine, the solution was heated under reflux for 14 hours.

After concentration, a suitable amount of 2-propanol was added to the residue and the precipitated crystals were recovered by filtration and dried to provide 6.48 g (84%) of (8aS)-2-benzyloxycarbonylhexahydropyrrolo[1,2-a]pyrazin-1,4-dione.

5 In 40 ml of tetrahydrofuran, 4.0 g of this product was dissolved and the solution was dropped into a suspension of 5.9 g of lithium aluminium hydride in 60 ml of tetrahydrofuran, followed by 14 hours' heating under reflux. The solution was cooled with ice, and excessive lithium aluminium hydride therein was decomposed by

10 addition of saturated aqueous sodium hydrogencarbonate solution. After addition of benzyloxycarbonyl chloride, the solution was stirred for an hour under cooling with ice and for further 2 hours at room temperature, followed by extraction with chloroform, washing with saturated brine, drying over anhydrous magnesium sulfate and

15 concentration. The residue was purified on silica gel column chromatography (chloroform : methanol = 25:1) to provide 2.77g (41%) of (8aS)-2-benzyloxycarbonyloctahydropyrrolo[1,2-a]pyrazine.

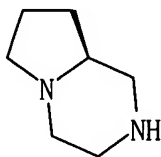
¹H-NMR(CDCl₃):7.36~7.35(m,5H),5.13(s,2H),4.28~4.10(m,2H),

20 3.10~3.05(m,1H),2.98(br s,2H),2.61(br s,1H),2.15~2.09(m,2H), 1.88~1.66(m,5H)

Mass,m/e:260(M⁺),91(base)

Step 102-E

25



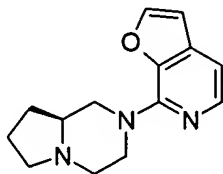
30 In 100 ml of methanol, 5.2 g of (8aS)-2-benzyloxycarbonyloctahydropyrrolo[1,2-a]pyrazine as obtained in above Step 102-D was dissolved, and to the solution 2.0 g of 20% palladium hydroxide on carbon was added, followed by an hour's stirring in hydrogen gaseous current. The catalyst was

35 separated by filtration and the solution was concentrated to provide

4.65 g (100%) of (8aS)-octahydropyrrolo[1,2-a]pyrazine.

Step 102-F

5



In 10 ml of ethylene glycol, 380 mg of (8aS)-octahydropyrrolo[1,2-a]pyrazine as obtained in above Step 102-E was dissolved and to which 270 mg of 7-chlorofuro[2,3-c]pyridine as obtained in Step 102-C and 202 mg of triethylamine were added, followed by an overnight's stirring at 140°C. After cooling, saturated aqueous sodium hydrogencarbonate solution was added to the mixture which then was extracted with chloroform and the organic layer was dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified on silica gel column chromatography (chloroform : methanol = 20:1) to provide 190 mg (39%) of 7-((8aS)-octahydropyrrolo[1,2-a]pyrazin-2-yl)furo[2,3-c]-pyridine.

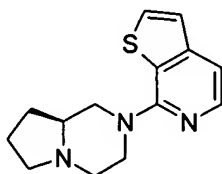
20

¹H-NMR(CDCl₃) δ: 7.95(d, J=5.4Hz, 1H), 7.63(d, J=2.3Hz, 1H), 6.95(d, J=5.4Hz, 1H), 6.72(d, J=1.9Hz, 1H), 4.80~4.76(m, 1H), 4.71~4.66(m, 1H), 3.325~3.14(m, 3H), 2.87~2.81(m, 1H), 2.44~2.40(m, 1H), 2.38~2.13(m, 2H), 1.96~1.84(m, 2H), 1.82~1.74(m, 1H), 1.56~1.51(m, 1H)
Mass, m/e: 243(M⁺), 147(base)

25

Production Example 103

30



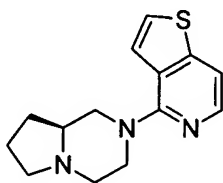
In the manner similar to Production Example 102, 7-((8aS)-octahydropyrrolo[1,2-a]pyrazin-2-yl)thieno[2,3-c]pyridine

35

was obtained.

¹H-NMR(CDCl₃)δ:8.12(d,J=5.4Hz,1H),7.57(d,J=5.4Hz,1H),
 7.31(d,J=5.4Hz,1H),7.23(d,J=5.4Hz,1H),4.44~4.40(m,1H),
 4.34~4.31(m,1H),3.27~3.26(m,1H),3.23~3.11(m,2H),
 2.92~2.86(m,1H),2.50~2.45(m,1H),2.27~2.21(m,2H),
 1.95~1.86(m,2H),1.83~1.76(m,1H),1.59~1.51(m,1H)
 Mass,m/e:259(M⁺),163(base)

10 Production Example 104

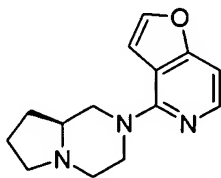


15

In the manner similar to Production Example 102,
 4-((8aS)-octahydropyrrolo[1,2-a]pyrazin-2-yl)thieno[3,2-c]pyridine
 was obtained.

20 ¹H-NMR(CDCl₃)δ:8.04(d,J=5.4Hz,1H),7.43~7.29(m,3H),
 4.17~4.12(m,1H),4.07~4.02(m,1H),3.28~3.22(m,1H),
 3.19~3.14(m,2H),2.94~2.88(m,1H),2.51(dt,J=2.7Hz,7.2Hz,1H),
 2.29~2.22(m,2H),1.94~1.85(m,2H),1.85~1.75(m,1H),
 1.56~1.50(m,1H)
 25 Mass,m/e:259(M⁺),107(base)

Production Example 105

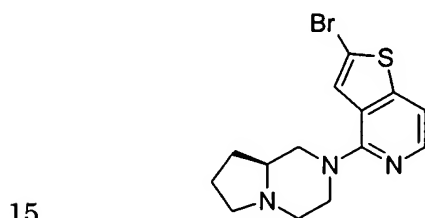


30

In the manner similar to Production Example 102,
 4-((8aS)-octahydropyrrolo[1,2-a]pyrazin-2-yl)furo[3,2-c]pyridine was
 35 obtained.

¹H-NMR(CDCl₃)δ:8.04(d,J=5.8Hz,1H),7.53(d,J=2.3Hz,1H),
 6.93(d,J=5.8Hz,1H),6.83(dd,J=0.8Hz,2.3Hz,1H),
 4.48(ddd,J=1.9Hz,2.7Hz,12.3Hz,1H),4.35~4.31(m,1H),
 3.30~3.23(m,1H),3.18~3.13(m,2H),2.91~2.85(m,1H),
 2.44~2.38(m,1H),2.25~2.13(m,2H),1.95~1.84(m,2H),
 1.82~1.50(m,2H)
 Mass,m/e:243(M⁺),147(base)

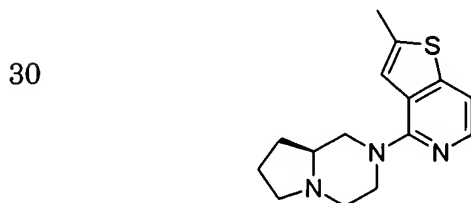
10 Production Example 106



In the manner similar to Production Example 102, 2-bromo-4-((8aS)-octahydropyrrolo[1,2-a]pyrazin-2-yl)thieno[3,2-c]pyridine was obtained.

20 ¹H-NMR(CDCl₃)δ:8.05(d,J=5.3Hz,1H),7.38(s,1H),
 7.17(d,J=5.8Hz,1H),4.06(td,J=2.3Hz,12.3Hz,1H),
 3.98~3.94(m,1H),3.25~3.14(m,3H),2.91~2.85(m,1H),
 2.51~2.47(m,1H),2.27~2.19(m,2H),1.94~1.82(m,2H),
 1.81~1.75(m,1H),1.54~1.49(m,1H)
 25 Mass,m/e:337(M⁺),96(base)

Production Example 107

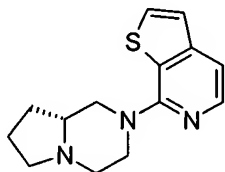


35 In the manner similar to Production Example 102,
 4-((8aS)-octahydropyrrolo[1,2-a]pyrazin-2-yl)-2-methylthieno[3,2-c]-

pyridine was obtained.

¹H-NMR(CDCl₃)δ:8.01(d,J=5.4Hz,1H),7.23~7.22(m,1H),
 7.03(d,J=1.2Hz,1H),4.07(td,J=2.3Hz,12.0Hz,1H),
 3.98(d,J=11.8Hz,1H),3.23~3.08(m,3H),2.90~2.84(m,1H),
 2.58(dd,J=1.2Hz,4.3Hz,3H),2.53~2.47(m,2H),2.37~2.27(m,2H),
 1.93~1.85(m,2H),1.81~1.75(m,1H);1.54~1.50(m,1H)
 Mass,m/e:273(M⁺),177(base)

10 Production Example 108

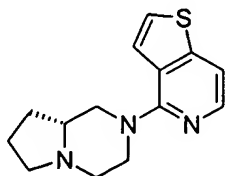


15

In the manner similar to Production Example 102,
 7-((8aR)-octahydropyrrolo[1,2-a]pyrazin-2-yl)thieno[2,3-c]pyridine
 was obtained.

¹H-NMR(CDCl₃)δ:8.13(d,J=5.4Hz,1H),7.57(d,J=5.4Hz,1H),
 7.31(d,J=5.4Hz,1H),7.24(d,J=5.4Hz,1H),
 4.41(td,J=2.3Hz,12.0Hz,1H),4.35~4.31(m,1H),
 3.24~3.15(m,3H),2.93~2.87(m,1H),2.51~2.45(m,1H),
 2.28~2.22(m,2H),1.94~1.87(m,2H),1.81~1.73(m,1H),
 1.56~1.52(m,1H)
 Mass,m/e:259(M⁺),163(base)

Production Example 109



30

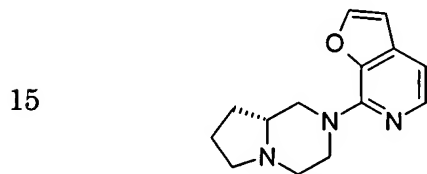
In the manner similar to Production Example 102,
 4-((8aR)-octahydropyrrolo[1,2-a]pyrazin-2-yl)thieno[3,2-c]pyridine

35

was obtained.

¹H-NMR(CDCl₃)δ:8.07(d,J=5.4Hz,1H),7.43~7.41(m,1H),
 7.37(d,J=5.4Hz,1H),7.33(dd,J=0.8Hz,5.8Hz,1H),
 4.17~4.13(m,1H),4.05(ddd,J=1.9Hz,5.0Hz,12.7Hz,1H),
 3.26(dt,J=2.7Hz,12.3Hz,1H),3.19~3.15(m,2H),
 2.95~2.89(m,1H),2.52(dt,J=2.7Hz,11.2Hz,1H),
 2.30~2.23(m,2H),1.94~1.87(m,2H),1.82~1.76(m,1H),
 1.56~1.49(m,1H)
 Mass,m/e:259(M⁺),163(base)

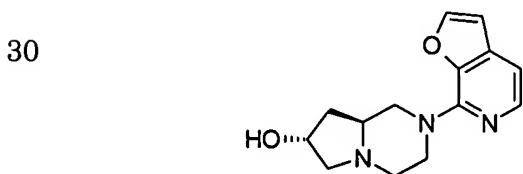
Production Example 110



In the manner similar to Production Example 102,
 7-((8aR)-octahydropyrrolo[1,2-a]pyrazin-2-yl)furo[2,3-c]pyridine was
 obtained.

20
¹H-NMR(CDCl₃)δ:7.93(d,J=5.0Hz,1H),7.62(d,J=1.9Hz,1H),
 6.94(d,J=5.4Hz,1H),6.70(d,J=2.3Hz,1H),4.79~4.74(m,1H),
 4.69~4.65(m,1H),3.324~3.12(m,3H),2.86~2.80(m,1H),
 2.43~2.39(m,1H),2.37~2.12(m,2H),1.95~1.83(m,2H),
 1.81~1.70(m,1H),1.56~1.49(m,1H)
 Mass,m/e:243(M⁺),147(base)

Production Example 111

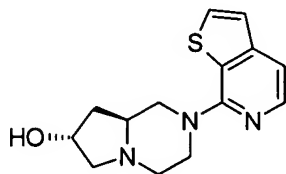


In the manner similar to Production Example 102,
 7-((7R,8aS)-7-hydroxyoctahydropyrrolo[1,2-a]pyrazin-2-yl)furo[2,3-c]-

pyridine was obtained.

¹H-NMR(CDCl₃)δ:7.93(d,J=5.4Hz,1H),7.62(d,J=2.3Hz,1H),
6.95(d,J=5.4Hz,1H),6.71(d,J=2.3Hz,1H),4.76~4.72(m,1H),
4.68~4.63(m,1H),4.56~4.52(m,1H),3.60~3.56(m,1H),
3.19~3.07(m,2H),2.78(dt,J=1.9Hz,10.4Hz,1H),
2.61~2.49(m,2H),2.23~2.19(m,1H),1.92~1.81(m,2H)
Mass,m/e:259(M⁺),147(base)

10 Production Example 112



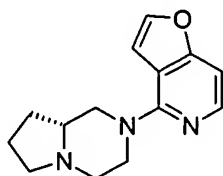
15

In the manner similar to Production Example 102,
7-((7R,8aS)-7-hydroxyoctahydropyrrolo[1,2-a]pyrazin-2-yl)thieno-
[2,3-c]pyridine was obtained.

¹H-NMR(CDCl₃)δ:8.11(d,J=5.4Hz,1H),7.57(d,J=5.4Hz,1H),
7.30(d,J=5.4Hz,1H),7.23(d,J=5.4Hz,1H),4.57~4.52(m,1H),
4.38~4.34(m,1H),4.30~4.25(m,1H),3.61~3.56(m,1H),
3.18(dt,J=3.1Hz,12.7Hz,1H),3.10(dt,J=2.7Hz,11.2Hz,1H),
2.86~2.81(m,1H),2.72~2.59(m,2H),2.28~2.24(m,1H),
1.93~1.81(m,2H)
Mass,m/e:275(M⁺),163(base)

25

Production Example 113



30

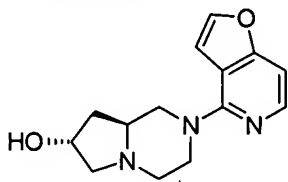
In the manner similar to Production Example 102,
4-((8aR)-octahydropyrrolo[1,2-a]pyrazin-2-yl)furo[3,2-c]pyridine was

35

obtained.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.04(d, $J=5.8\text{Hz}$, 1H), 7.53(d, $J=2.3\text{Hz}$, 1H),
 6.93(dd, $J=0.8\text{Hz}$, 5.8Hz, 1H), 6.83~6.82(m, 1H), 4.50~4.46(m, 1H),
 4.35~4.31(m, 1H), 3.27(dt, $J=3.1\text{Hz}$, 12.3Hz, 1H),
 3.18~3.14(m, 2H), 2.92~2.86(m, 1H),
 2.41(dt, $J=3.4\text{Hz}$, 11.2Hz, 1H), 2.25~2.15(m, 2H),
 1.95~1.85(m, 2H), 1.82~1.75(m, 1H), 1.56~1.48(m, 1H)
 Mass, m/e : 243(M^+), 147(base)

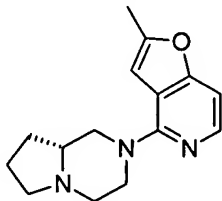
Production Example 114



In the manner similar to Production Example 102,
 4-((7R,8aS)-7-hydroxyoctahydropyrrolo[1,2-a]pyrazin-2-yl)furo[3,2-c]-
 pyridine was obtained.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.04(d, $J=5.8\text{Hz}$, 1H), 7.54(d, $J=2.3\text{Hz}$, 1H),
 6.92(dd, $J=1.2\text{Hz}$, 5.8Hz, 1H), 6.82(dd, $J=0.8\text{Hz}$, 2.3Hz, 1H),
 4.57~4.53(m, 1H), 4.43(ddd, $J=1.9\text{Hz}$, 2.7Hz, 11.9Hz, 1H),
 4.32~4.27(m, 1H), 3.60~3.56(m, 1H), 3.25~3.20(m, 1H),
 3.11~3.07(m, 1H), 2.86~2.81(m, 1H), 2.66~2.52(m, 2H),
 2.26~2.23(m, 1H), 1.89~1.82(m, 2H)
 Mass, m/e : 259(M^+), 147(base)

Production Example 115

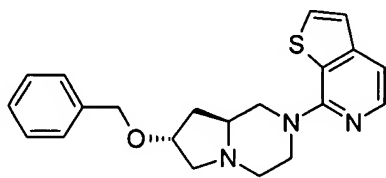


In the manner similar to Production Example 102,
 4-((8aR)-octahydropyrrolo[1,2-a]pyrazin-2-yl)-2-methylfuro[3,2-

clpyridine was obtained.

¹H-NMR(CDCl₃)δ:7.97(d,J=5.8Hz,1H),
 6.84(dd,J=0.8Hz,5.8Hz,1H),6.40(s,1H),4.42~4.38(m,1H),
 4.28~4.21(m,1H),3.24~3.12(m,3H),2.86~2.80(m,1H),
 2.43(d,J=1.2Hz,3H),2.42~2.35(m,1H),2.26~2.13(m,2H),
 1.93~1.85(m,2H),1.80~1.73(m,1H),1.55~1.48(m,1H)
 Mass,m/e:257(M⁺),161(base)

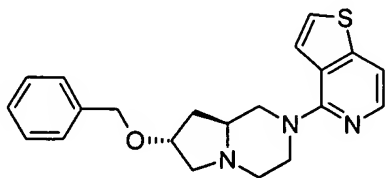
10 Production Example 116



In the manner similar to Production Example 102,
 7-((7R,8aS)-7-benzyloxyoctahydropyrrolo[1,2-a]pyrazin-2-yl)thieno-
 [2,3-c]pyridine was obtained.

¹H-NMR(CDCl₃)δ:8.11(d,J=5.8Hz,1H),7.56(d,J=5.4Hz,1H),
 7.34~7.22(m,7H),4.49(dd,J=1.6Hz,3.5Hz,2H),4.39~4.35(m,1H),
 4.30~4.26(m,1H),3.56~3.52(m,1H),3.20~3.08(m,2H),
 2.85~2.80(m,1H),2.62~2.53(m,2H),2.38~2.34(m,1H),
 1.99(ddd,J=1.5Hz,7.2Hz,13.1Hz,1H),1.81~1.75(m,1H)
 Mass,m/e:365(M⁺),91(base)

Production Example 117

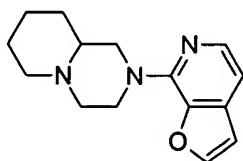


In the manner similar to Production Example 102,
 4-((7R,8aS)-7-benzyloxyoctahydropyrrolo[1,2-a]pyrazin-2-yl)thieno-

[3,2-c]pyridine was obtained.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 8.06(d, $J=5.8\text{Hz}$, 1H), 7.41~7.26(m, 8H),
 4.53~4.4(m, 2H), 4.25~4.22(m, 1H), 4.10(td, $J=2.3\text{Hz}$, 11.9Hz, 1H),
 4.00(dd, $J=2.7\text{Hz}$, 12.7Hz, 1H), 3.56~3.52(m, 1H),
 3.21~3.14(m, 1H), 3.11~3.07(m, 1H), 2.85~2.80(m, 1H),
 2.66~2.56(m, 2H), 2.37(dd, $J=5.4\text{Hz}$, 9.6Hz, 1H),
 1.97(ddd, $J=1.5\text{Hz}$, 6.2Hz, 13.1Hz, 1H), 1.79~1.71(m, 1H)
 Mass, m/e : 365(M^+), 163(base)

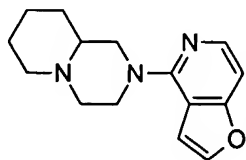
Production Example 118



In the manner similar to Production Example 102,
 7-octahydropyrido[1,2-a]pyrazin-2-ylfuro[2,3-c]pyridine was obtained.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 7.95(d, $J=5.4\text{Hz}$, 1H), 7.62(d, $J=2.3\text{Hz}$, 1H),
 6.95(d, $J=5.4\text{Hz}$, 1H), 6.71(d, $J=2.3\text{Hz}$, 1H), 4.65~4.58(m, 1H),
 4.49~4.43(m, 1H), 3.30~3.20(m, 1H), 2.94~2.77(m, 3H),
 2.47~2.38(m, 1H), 2.15~2.04(m, 2H), 1.87~1.77(m, 1H),
 1.73~1.64(m, 3H), 1.40~1.29(m, 2H)
 Mass, m/e : 257(M^+), 110(base)

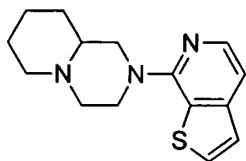
Production Example 119



In the manner similar to Production Example 102,
 4-octahydropyrido[1,2-a]pyrazin-2-ylfuro[3,2-c]pyridine was obtained.

¹H-NMR(CDCl₃)δ:8.04(d,J=5.8Hz,1H),7.53(d,J=2.3Hz,1H),
 6.92(dd,J=0.7Hz,5.8Hz,1H),6.80(dd,J=1.2Hz,2.3Hz,1H),
 4.30~4.22(m,1H),4.20~4.13(m,1H),
 3.29(dt,J=2.7Hz,12.3Hz,1H),
 2.94~2.81(m,3H),2.46~2.37(m,1H),2.15~2.04(m,2H),
 1.88~1.75(m,1H),1.75~1.57(m,3H),1.42~1.24(m,2H)
 Mass,m/e:257(M⁺),110(base)

10 Production Example 120



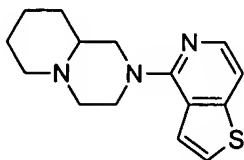
15

In the manner similar to Production Example 102,
 7-octahydropyrido[1,2-a]pyrazin-2-ylthieno[2,3-c]pyridine was
 obtained.

20 ¹H-NMR(CDCl₃)δ:8.12(d,J=5.4Hz,1H),7.57(d,J=5.4Hz,1H),
 7.31(d,J=5.4Hz,1H),7.23(d,J=5.4Hz,1H),4.32~4.24(m,1H),
 4.16~4.09(m,1H),3.26(dt,J=2.7Hz,12.3Hz,1H),
 2.95~2.82(m,3H),2.49(dt,J=3.1Hz,12.0Hz,1H),
 2.20~2.09(m,2H),1.86~1.78(m,1H),1.74~1.60(m,3H),
 25 1.40~1.31(m,2H)
 Mass,m/e:273(M⁺),110(base)

Production Example 121

30



In the manner similar to Production Example 102,
 35 4-octahydropyrido[1,2-a]pyrazin-2-ylthieno[3,2-c]pyridine was

obtained.

¹H-NMR(CDCl₃)δ:8.07(d,J=5.4Hz,1H),7.41(d,J=5.4Hz,1H),
 7.37(d,J=5.4Hz,1H),7.33(d,J=5.4Hz,1H),4.01~3.94(m,1H),
 5 3.87~3.81(m,1H),3.26(dt,J=2.7Hz,12.3Hz,1H),
 2.95~2.83(m,3H),2.52(dt,J=3.0Hz,11.6Hz,1H),
 2.24~2.10(m,2H),1.87~1.75(m,1H),1.73~1.56(m,3H),
 1.42~1.29(m,2H)
 Mass,m/e:273(M⁺),110(base)

10

Formulation Example: Tablets:

	mg/tablet
Active ingredient	5.0
Starch	10.0
Lactose	73.0
Carboxymethyl cellulose-calcium	10.0
Talc	1.0
Magnesium stearate	1.0
	100.0

The active ingredient was pulverized to a particle size not
 greater than 70μm, to which starch, lactose and carboxymethyl
 cellulose-calcium were added and mixed thoroughly. To the above
 15 powdery mixture, 10% starch paste was added, agitated and mixed to
 prepare granules. After drying, the particle size of the granules was
 dressed to around 1000μm, with which talc and magnesium stearate
 were mixed and tabletted.